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Re: For Your Information Submission:

The enclosed information is submitted on behalf of Dow Corning Corporation, Midland, Michigan, 48686-0994, on a For-Your-Information (FYI) basis as a follow-up to submissions made concerning hexamethyldisiloxane (HMDS), which chemical substance was the subject of a health and safety data rule issued under Section 8(d) of the Toxic Substances Control Act (TSCA) and with an effective date of June 14, 1993 (sunset date June 30, 1998), as codified at 40 CFR 716 (Health and Safety Data Reporting). The information presented in this submission was generated as part of our Siloxane Research Program. This program was the subject of a memorandum of understanding, dated April 9, 1996, between Dow Corning and EPA.

Listed Chemical Substance:

107-46-0 Hexamethyldisiloxane (HMDS)

Final Study Report:

Study of Hexamethyldisiloxane (HMDS) in the Rat Following a 14-Day Nose-Only Vapor Inhalation Exposure to HMDS Followed by an Exposure to ^{14}C-HMDS on Day 15, Additionally Studied is a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

Dow Corning Corporation
2006-I0000-55952
December 7, 2006

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303883

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For purposes of this TSCA For-Your-Information (FYI) submission, the general INTERNAL designation on the attached health and safety report is waived by Dow Corning.

If you require further information regarding this submission, please contact Michael Thelen, Manager of U.S. EPA Regulatory Affairs, at 989-496-4168 or at the address provided herein.

Sincerely,

Kathleen P. Plotzke
Director, Health and Environmental Sciences
(989) 496-8046

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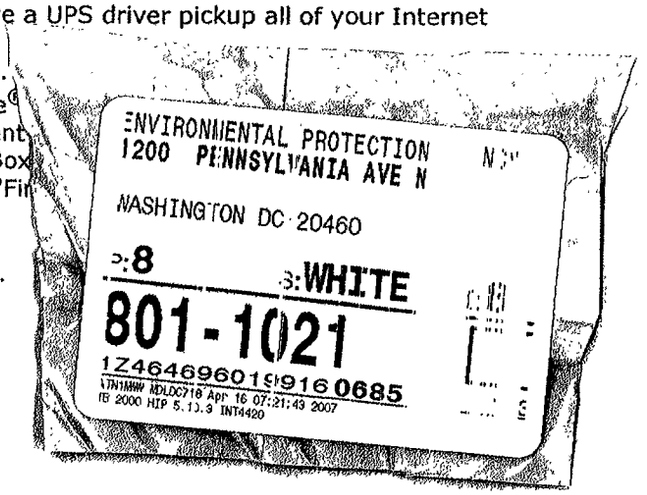

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DOW CORNING CORPORATION
HEALTH & ENVIRONMENTAL SCIENCES
TECHNICAL REPORT

Report Number:	2006-I0000-55952
Title:	Study of Hexamethyldisiloxane (HMDS) in the Rat Following a 14-Day Nose-Only Vapor Inhalation Exposure to HMDS Followed by an Exposure to ^{14}C-HMDS on Day 15, Additionally Studied is a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS
Study Number:	9829-101
Test Article:	Hexamethyldisiloxane (HMDS)
Study Director:	Jeremy A. Durham, B.S. Senior Chemist
Sponsor:	Dow Corning Corporation
HES Management: Team Leader, Toxicology	Paul A. Jean, Ph.D.
Testing Facility:	Dow Corning Corporation Health and Environmental Sciences Auburn, MI 48611
Study Completion Date:	December 7, 2006
Security Statement:	**Dow Corning Internal.** This report may be reproduced and shared with any Dow Corning employee. The director of the issuing department must approve distribution outside the corporation. When this INTERNAL report is no longer needed, it must be destroyed in a manner that safeguards against unauthorized disclosure.

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ABSTRACT

The purpose of this study was to evaluate absorption, distribution, metabolism and excretion (ADME) and kinetic parameters of hexamethyldisiloxane (HMDS) in male Fischer 344 rats following a single exposure to 5000 ppm ^{14}C HMDS and fourteen days of exposure to a target concentration of 5000 ppm HMDS followed by a single exposure to 5000 ppm ^{14}C-HMDS on exposure day fifteen. Male rats for the single exposure were exposed via nose-only inhalation, six hours a day, for one day to an average concentration of 4989 ± 189.6 ppm of ^{14}C-HMDS. Male rats for the repeat exposure were exposed via nose-only inhalation, six hours a day, for fourteen consecutive days, to an average concentration of 4999 ± 98.0 ppm HMDS, followed by a single exposure to 5365 ± 66.6 ppm of ^{14}C-HMDS on day fifteen. On day one of the single exposure and day fifteen of the repeat exposure, animals were euthanized, at predetermined time points during and following the exposure period, for collection of blood, tissues and excreta. An additional group of animals was euthanized immediately following the exposure on day one of the single exposure and day fifteen of the repeat exposure for determination of total ^{14}C body burden.

In the body burden animals, approximately 3.6 ± 0.24% and 3.8 ± 0.86% of the total radioactivity was retained at the end of the exposure period for the single exposure and repeat exposure groups, respectively. Excreta animals were placed in glass metabolism cages following the radiolabeled exposure for collection of urine, feces and expired air up to 168-hours post exposure. Samples were processed and analyzed for radioactivity and parent HMDS content. Following day one of a single exposure and day fifteen repeat exposure radioactivity was measured in the carcass and parent HMDS and total radioactivity were measured in the blood, and selected tissues (brain, kidneys, testes, liver, lung, and perirenal fat).

The percentage of the recovered dose found in urine was ~46 and 64% for the single and repeated exposures, respectively. Expired volatiles accounted for ~46% and 28% of the recovered radioactivity following the single and repeated exposures, respectively. Fecal elimination was ~2% for the single and repeated exposures. Collected tissues accounted for less than 0.2% of the recovered dose and radioactivity remaining in the carcass was ~ 3% of the recovered dose for both

the single and repeated exposures. The overall mass balance of radioactivity, as a percent of the body burden dose in the single and repeated exposure groups was 114 and 128%, respectively. The majority of the radioactivity (~80%) was eliminated by 24 h post-exposure.

All tissues contained both parent HMDS and metabolites. In tissues (less than 0.2% of the recovered radioactivity) the majority of radioactivity, within the first 24 hours following exposure could be attributed to parent, with this decreasing over time to a small fraction attributable to parent from 24 to 168 h post-exposure. Parent was eliminated from blood and tissues at a faster rate than total radioactivity. Following a single exposure, the percentage of the total radioactivity attributed to metabolites ranged from 61.37% to 98.35%; liver (98.35%), blood (94.69%), brain (88.35%), lung (84.99%), testes (66.64%) and kidney (61.37%). In fat approximately 17% was attributed to metabolites following the single exposure group. Following repeated exposures, the percentage of the total radioactivity attributed to metabolites in blood and tissues ranged from 38.12% to 97.49%; liver (97.49%), blood (97.09%), brain (89.04%), lung (77.48%), testes (55.66%) and kidney (38%). The percentage of parent HMDS in fat following the single exposure was ~83 % and that in kidney was ~39%, in testes 33% and in lung 15%. Following repeated exposure the percentage of parent HMDS increased to ~62% in kidney, increased to 44% in testes and increased to ~23% in lung tissue.

Elimination half-lives for radioactivity were similar between the single and repeated exposure groups and this was also true for the half-lives for parent HMDS. The terminal half-life of elimination of radioactivity from the blood and tissues (excluding fat) was multi-phasic with the majority of the radioactivity eliminated within 24 h post-exposure. The terminal half-life of elimination of radioactivity in blood was ~36 and 39 h for the single and repeated exposures, respectively. Half-lives of elimination of over 40 h were measured in liver, lung and testes after the single exposure and in liver, lung, testes and brain after repeated exposures. In general, half-lives of elimination were 1 to 3 fold faster for parent HMDS than radioactivity; notable was the faster elimination half-life of HMDS from lung tissue. In blood, parent HMDS levels were not measurable beyond 24 h post-exposure for single and repeated exposure and in lung tissue parent HMDS levels were not measurable beyond 72 h post-exposure for the single exposure only.

Approximately 53% of the total radioactivity in expired volatiles was attributed to metabolites for the single exposure. The maximum concentration of radioactivity found in expired volatiles was in the first 0-1 hour collection interval following the single and repeated exposures. Following a single exposure the maximum concentration of radioactivity was found in the 12-24 h post-exposure interval for feces and in the 6-12 h post-exposure interval in urine. The highest concentration of $^{14}CO_2$ was found in the first interval, 0-24 h post-exposure. Half-lives of elimination for radioactivity were similar for expired volatiles, feces, urine and CO_2 within the single (range of 16-22 h) or repeated (range of 15-19 h) groups.

Urine analyses demonstrated that several peaks were present, but none corresponded to the retention time of parent. Primary metabolites detected were 1,3-bis(hydroxymethyl)tetramethyldisiloxane and an unknown metabolite with retention times of 25 and 26.5 minutes, respectively. Other metabolites that were detected at greater than 4% were dimethylsilanediol and trimethylsilanol.

Data from this study supports the observations in other studies with HMDS where an alpha 2u-globulin mechanism for renal toxicity in male rats has been noted (Cassidy et al., 2001; Jovanovic et al., 2005). The percentage of total radioactivity in kidney as parent HMDS, increased from ~39% to ~62% following the single and repeated exposure, respectively. The ratio of parent AUC in kidney to parent AUC in blood was ~30-fold higher than the same ratio calculated for liver tissue. This observation is consistent with the hypothesis that HMDS is an alpha 2u-globulin ligand and with a previous observation of increased alpha 2u-globulin in the kidney after exposure to HMDS.

The data from these experiments provide insight into the pharmacokinetics of HMDS. After single exposure and repeat exposure to 5000 ppm HMDS, approximately 4% of the dose was retained. Parent HMDS was measured in blood and tissues; brain, fat, kidney, liver, lung and testes and the highest concentrations were found in fat and kidney. Elimination of radioactivity from blood and tissues (excluding fat) was multi-phasic, with the majority of the radioactivity eliminated within 24 h post-exposure. The majority of systemically absorbed HMDS was eliminated in the urine or expired volatiles. Urinary elimination was entirely polar metabolites. Considering the effective removal of HMDS through metabolism and exhalation, accumulation in the body after repeated exposures is unlikely despite its high lipophilicity. The data from this study will be used to further refine PBPK models for HMDS.

GLP COMPLIANCE STATEMENT

This study was conducted in compliance with Environmental Protection Agency Toxic Substances Control Act Good Laboratory Practice Standards 40 CFR part 792, except the feed and water analysis which were not performed under GLP's.

The Dow Corning Health and Environmental Sciences (HES) Quality Assurance Unit monitored the study in accordance with Dow Corning HES Standard Operating Procedures.

Jeremy A. Durham, B.S.
Study Director

December 7, 2006
Date

Paul A. Jean, Ph.D.
Team Leader, Toxicology

07 Dec 06
Date

QUALITY ASSURANCE STATEMENT

Title: Study of Hexamethyldisiloxane (HMDS) in the Rat Following a 14-Day Nose-Only Vapor Inhalation Exposure to HMDS Followed by an Exposure to ^{14}C-HMDS on Day 15, Additionally Studied is a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

Study Number: 9829-101

This study has been audited by the Dow Corning Corporation Health and Environmental Sciences Quality Assurance Unit according to approved Standard Operating Procedures to assure that the raw data are accurately reflected within this final report. The following are the inspection dates and the dates inspection findings were reported.

Dates of Inspection	Phase Inspected	Findings Reported to Study Director	Findings Reported to Management
31 Mar – 01 Apr 03	Draft Protocol Review	01 Apr 03	01 May 03
13 Jun 03	Radiochemical Purity	16 Jun 03	19 Jun 03
16 Jun 03	Patency Checks	16 Jun 03	19 Jun 03
23 Jun 03	Tissue Collection	24 Jun 03	01 Jul 03
02 Oct 03	Tissue Processing	02 Oct 03	03 Oct 03
27 Mar 06	Animal Information Data	28 Mar 06	28 Mar 06
27-28 Mar 06	Main Study Binder	28 Mar 06	28 Mar 06
28 Mar 06	Inhalation Binder	28 Mar 06	28 Mar 06
29 Mar 06	Exposure Data	29 Mar 06	29 Mar 06
30 Mar 06	HPLC Urine Data	30 Mar 06	30 Mar 06
24-26 Apr 06	Parent Binders: SE1D, SE1E, E01a	26 Apr 06	26 Apr 06

24-26 Apr 06	Parent Binders: E01f/g, E01b, E01d, E01c/f	26 Apr 06	26 Apr 06
26-28 Apr 06	Charcoal Analysis, Fat Analysis & DC Balance Forms	28 Apr 06	28 Apr 06
26-28 Apr 06	Binders: E01G, SE1A, SE1B	28 Apr 06	28 Apr 06
12-15 Jun 06	Radioactivity Binder	15 Jun 06	15 Jun 06
28-31 Mar, 24-28 Apr and 12-16 Jun 06	Draft Report (Excluding App. D, Statistics)	16 Jun 06	16 Jun 06
18-19 Sep 06	Draft Report: App. D, Statistics	19 Sep 06	19 Sep 06

Lisa Drottar
Team Leader, Quality Assurance
Dow Corning Corporation
Health & Environmental Sciences

07 Dec 2006
Date

APPROVAL SIGNATURES

This report consists of pages 1 through 198 including Tables I through XVIII, Figures 1 through 17, and Appendices A through D.

Jeremy Durham

December 7, 2006

Jeremy A. Durham, B.S.
Study Director

Date

Debra A. McNett

Dec. 7, 2006

Debra A. McNett, B.S.
Contributing Scientist

Date

Jeanne Y. Domoradzki

07 December 2006

Jeanne Y. Domoradzki, Ph.D.. DABT
Contributing Scientist

Date

Paul A Jean

07 Dec 06

Paul A. Jean, Ph.D.
Team Leader, Toxicology

Date

STUDY INFORMATION

Study Initiation Date:	5/20/2003
Experimental Start Date:	6/02/2003
Experimental Termination Date:	10/31/2003
Study Completion Date:	December 7, 2006
Study Director:	Jeremy A. Durham, B.S.
Sponsor:	Dow Corning Corporation
HES Management:	Paul A. Jean, Ph.D.
Attending Veterinarian:	James W. Crissman, D.V.M., Ph.D., D.A.C.V.P.
Contributing Scientists:	Debra A. McNett, B.S. Jeanne Y. Domoradzki, Ph.D., DABT
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Key Study Personnel:	Joseph M. Tobin, B.S. Brian J. Marinik, B.S., M.B.A.

I. OBJECTIVE

The purpose of this study was to evaluate the absorption, distribution, metabolism and excretion (ADME) of parent HMDS and radioactivity in male Fischer 344 rats following both a single and repeated nose-only exposure design to un-labeled and ^{14}C-labeled HMDS at a target concentration of 5000 ppm.

II. MATERIALS AND METHODS

A. TEST SYSTEM

Species:	*Rattus norvegicus*
Strain:	CDF®(F-344)/CrlBR
Source:	Charles River Breeding Laboratories, Inc.
	Raleigh, NC 27610
Age:	67-74 days at initiation of exposure
Body weight:	201-242.7 grams at initiation of exposure
Sex and number used:	
Repeat exposure	55 males
Single exposure	55 males
Total	110 males

1. Identification

Upon receipt in the Toxicology Department, each animal received a Q number. At the end of the quarantine period, non-cannulated and cannulated rats were weighed, randomized and uniquely identified by a metal ear-tag displaying the animal number as documented in the study records. Individual cage tags were placed on the outside of each cage.

2. Justification for Selection of Test System

This species and strain of animal is recognized as appropriate for toxicity studies and is recommended in EPA test guidelines. Fischer 344 male rats have previously been used in pharmacokinetic and metabolism studies of various silicone materials, and data obtained in those studies can be used as historical data. Previous chronic exposure to this material has shown toxicity in male Fischer 344 rats and therefore only male rats were used in this study. The number of animals used provided adequate statistical power.

3. Housing

Upon receipt, animals were individually housed in suspended wire-mesh bottom stainless-steel cages. The cages were elevated above urine and feces collection pans containing Bed-O'Cobs® bedding. Following release from quarantine, animals were transferred into new suspended wire-mesh bottom stainless-steel cages depending on group assignment. During each exposure period animals were individually positioned in nose-only restraint cones without access to food or water. Following each exposure, animals were returned to their pre-exposure housing cages.

Animals were housed in environmentally controlled animal rooms with controls set to maintain temperatures at 64-79°F (18-26°C) and relative humidity at 30-70%. Temperature and relative humidity were monitored continuously. Air handling units for the room were set to provide 10-15 air changes per hour. Fluorescent lighting controlled by light timers provided illumination for a 12-hour light/dark photoperiod. The targeted photoperiod was interrupted periodically during sample collections. Such interruptions were considered necessary for the conduct of the study and were not considered to have an impact on the study outcome. Airflow and animal condition in the metabolism cages were monitored at least twice a day (am/pm) during the experiment. Airflow in the metabolism cages was kept in the range of 550-600 ml/min. Cage temperature was checked at the time of sample collection and was kept in the range of 68-73°F.

4. Diet

Purina® Certified Rodent Chow #5002, was offered *ad libitum* except while animals were loaded in the nose-only restraint tubes. Analysis of the certified feed for the presence of heavy metals and pesticides was performed and provided by the manufacturer. The diet was considered acceptable for use on study.

5. Drinking Water

Municipal water, further purified by reverse osmosis was available *ad libitum* except while the animals were loaded in restraint cones. The water was monitored on at least a semi-annual basis to determine compliance with the U.S.E.P.A. drinking water standards. The most recent analysis did not indicate any contaminants in the water at levels expected to interfere with the integrity of the study.

6. Animal Welfare Act Compliance

This study complied with all applicable sections of the final rules of the Animal Welfare Act regulations (9 CFR, Part 1, 2 and 3) and was approved by the Laboratory Animal Care and Use Committee (LACUC) before animals were ordered.

B. TEST ARTICLE INFORMATION

Test Article I

Test article characterization was done in compliance with the EPA Toxic Substances Control Act (TSCA), and Good Laboratory Practice Standards (40 CFR Part 792).

The characterization of the unlabeled test article (HMDS) identified below included a visual inspection, purity by gas chromatography (GC) with thermal conductivity detector (TCD) and GC with mass spectrometry (MS) to verify the identity of the major component as HMDS (HES Study Number 9242). Records of characterization are maintained in the HES Archive. Documentation of study director review is kept in the study files. Any remaining test article was disposed by the study personnel.

Identification:	Hexamethyldisiloxane (HMDS supplied as Dow Corning® OS-10)
Lot Number:	0000220953
CAS Number:	107-46-0
Source:	Dow Corning Corporation
Physical Description:	Colorless Liquid (as specified in PDM)
Stability:	Stable (as specified in PDM)
Solubility:	Ethanol, acetone, methanol, ethyl ether, toluene, heptane(as specified in PDM)
Chemical Characterization:	HES Study Number 9242
Expiration date:	February 3, 2004
Purity:	≥99%
Storage Conditions:	Room temperature
Reserve Sample:	A sample was retained in the HES Test Article Archives, Dow Corning Corporation Auburn, MI 48611

Test Article II

Chemical identity and radiochemical purity of the labeled test article (^{14}C-HMDS) was determined using gas chromatography/mass spectrometry (GC/MS) and high performance liquid chromatography (HPLC) with a radioactivity flow-through detector (RAD), respectively (HES study No. 9832). Records of characterization are maintained in the HES Archive. Documentation of study director review was placed in the study records. Any remaining test article was disposed by the study personnel.

Identification:	^{14}C-Hexamethyldisiloxane (HMDS)
Lot Number:	17521-119D
Source:	Dow Corning Corporation
Specific Activity:	4.269 mCi/g
Physical Description:	Colorless Liquid (as specified in PDM)
Stability:	Stable (as specified in PDM)
Expiration date:	February 03, 2004

Purity:	≥98%
Solubility:	Ethanol, acetone, methanol, ethyl ether, toluene, heptane, ACN, n-pentane, toluene.
Chemical Characterization:	HES Study Number 9832
Storage Conditions:	Freezer (-80 ± 10°C) until final dilution with unlabelled HMDS, then at room temperature
Reserve Sample:	A sample was retained in the HES Test Article Archives, Dow Corning Corporation Auburn, MI 48611

This ^{14}C-HMDS solution was further diluted with unlabelled HMDS solution three days prior to dosing on day 15 of the repeat exposure and three days prior to dosing of the single exposure. After the final dilution of ^{14}C-HMDS, the dosing solution was stored at room temperature; following the exposure the remaining solution was stored at (-80 ± 10°C).

C. ROUTE AND RATIONALE OF TEST ARTICLE ADMINISTRATION

Route

For groups 3, 4, 5 and 6, test article was administered via nose-only inhalation for fifteen consecutive exposures to an air atmosphere containing HMDS (days 1-14) or ^{14}C-HMDS (day 15) vapor. For groups 9, 10, 11 and 12, test article was administered via nose-only inhalation for a single exposure to an air atmosphere containing ^{14}C-HMDS vapor.

Rationale

The route is a potential relevant route of exposure for humans and is an accepted method of administration in pharmacokinetics and metabolism studies.

1. Inhalation Exposure Equipment

Nose-only vapor inhalation exposures were conducted in a specially designed Polyvinyl chloride (PVC) chamber similar to the Cannon style flow past nose-only exposure chamber. The chamber was operated at a slight positive pressure within a containment booth, which was operated at a negative pressure preventing outward leakage of the test

atmosphere into the room. Using a Magnehelic® gauge to continuously monitor the chamber pressure during each exposure period, a minimum of one reading was recorded during each exposure period. Chamber air was supplied by a Nash compressor and filtered with a series of Balston® filters model A912. During the exposures, airflow through the chamber was maintained at a rate providing a minimum of 500 ml/minute of air to each port on the chamber. Efforts were made to maintain the temperature in the chamber at 23 ± 3°C and the relative humidity between 20-70%. Chamber temperature and humidity were monitored continuously using a temperature/humidity meter placed in an enclosed plastic cone, which was attached to the chamber. Airflow was monitored continuously using an in-line flow meter located on the inlet side of the exposure chamber. Temperature, humidity and airflow were manually recorded at approximately thirty-minute intervals throughout the duration of each exposure. Oxygen levels were evaluated prior to start of the exposures using a Bacharach model Oxor® II oxygen monitor, while the chamber was operated at nominal conditions.

During each exposure, animals were individually positioned in polycarbonate restraint tubes designed to directly attach to the nose-only exposure chamber. The cones were sealed using plastic bags designed with closable seals. Urine and feces were collected in the bags and either discarded following each exposure or collected for processing. Animals were acclimated to restraint cones on four consecutive days prior to initiation of the first exposure for 1, 2, 4 and 6 hours respectively.

2. Generation of Exposure Atmosphere

Test article vapor was generated using a glass J-tube vapor generating system containing glass beads, a fluid metering device, and a carrier gas stream (compressed air from a Nash air compressor passed through a series of Balston® brand filters model A912). The J-tube was wrapped with heating tape and maintained at 90-110°C during each exposure period to promote test article vaporization into the carrier gas stream. A Fluid Metering Incorporated (FMI) pump was used to draw test article from a reservoir and meter into the J-tube at a rate predetermined to yield a targeted chamber concentration. The carrier gas stream swept the vapor into the chamber where it was distributed to the animals. The

airflow exiting the J-tube, approximately 28 liters per minute (LPM), comprised the total airflow supplied to the exposure chamber.

Prior to initiation of the exposure, homogeneity of the HMDS vapor distribution within the chamber atmosphere was evaluated using a Varian model 3400 gas chromatograph (GC). The chamber was operated at nominal environmental conditions during the evaluation. Three samples of the chamber atmosphere were collected from a representative port at each level of the exposure chamber and analyzed by the calibrated GC. The results of this analysis were used to determine temporal variation of HMDS distribution within the exposure chamber.

3. Chamber Atmosphere Monitoring

The concentration of test article in the chamber atmosphere during each exposure period was determined using a Varian model 3400 GC equipped with a Flame Ionization Detector (FID). Prior to the first day of exposure, the GC methodology was established. A calibration curve was constructed from five different test article vapor concentrations, which bracketed the expected range of the targeted exposure concentration. Two calibration gas bag standards were prepared for each calibration level with each bag sampled in duplicate, providing a total of twenty calibration points. The acceptance criteria for the calibration curve included the following:

- A coefficient of variation of ≤5% for all of the bag standard samples within a calibration level
- A linear regression analysis correlation coefficient (r^2) of ≥0.98
- A ≤10% difference between the prepared bag standard concentration and the calculated bag standard concentration derived from the linear regression equation of the calibration curve.

Instrument calibration was checked prior to each exposure by analysis of a gas bag standard within the range of the calibration curve.

Chamber atmosphere was sampled during each exposure period using a vacuum pump to draw the chamber atmosphere through a Teflon® sample line to the GC. At the GC,

sample passed through a gas-sampling loop, and was injected onto the column a minimum of twice per hour during each exposure period. Actual measured chamber concentrations during each exposure were calculated using the individual area count responses of each analysis and the linear regression equation from the GC calibration. Nominal concentration was determined utilizing the following equation:

$$\text{Nominal Conc.} = \frac{\text{Amount of test article used (g)}}{\text{Total volume of air passed through the chamber (L)}} \times \frac{24.6 \times 10^6 \text{ (L/mole)}}{\text{Molecular weight of test article (g/mole)}}$$

Where the amount of test article used was determined using the difference between pre- and post-exposure weights of the test article reservoir (grams), and the total volume of air passed through the chamber was determined by the mean chamber airflow rate during the exposure (LPM) multiplied by the exposure duration (minutes).

D. EXPERIMENTAL DESIGN

1. Randomization

Animals for the repeat exposures were ordered at a different time than the animals for the single exposure so that the age and weight requirements were satisfied. Upon release from quarantine, approved rats were weighed and randomized into test groups based on a weight stratified randomization process. Cannulated and non-cannulated animals were randomized separately into appropriate groups. All animals were within ± 20 % of the mean body weight for the group to which they were assigned. Animals not selected for the study were returned to the Animal Resources personnel.

2. Group Assignments

This study was completed in two parts the first, a fifteen day repeated exposure consisted of four (4) exposure groups and two (2) control groups. Animals in the control groups (1 and 2) remained in housing cages during the exposure periods and were not exposed to the test article. Groups 3, 4, 5 and 6 received a six hour per day exposures, for fourteen consecutive days to a target concentration of HMDS followed by a single six hour exposure to ^{14}C-HMDS on day 15. The second part of the study, a single exposure

consisted of four (4) exposure groups and two (2) control groups. Animals in the control groups (7 and 8) remained in housing cages during the exposure period and were not exposed to the test article. Groups 9, 10, 11 and 12 received a six hour exposure to ^{14}C-HMDS. Each group contained male Fischer 344 rats with animals in groups 2, 3, 6, 8, 9 and 12 containing jugular cannulas. Group assignments and handling are outlined below:

a. Excreta Control (Groups 1 and 7)

On day 15 of the repeat exposure and on the day of the single exposure, the control animals were transferred to individual glass metabolism cages. Animals were maintained in these cages until their scheduled sacrifice time. Urine and feces were collected from these animals up to the time of euthanasia and either processed or discarded. These control animals served as background control for the distribution and excreta group animals during the repeat or single exposures. Animals were sacrificed as close as possible to the 168-hour post exposure time point for collection of tissues.

b. Body Burden Control (Groups 2 and 8)

These control animals served as background control for the body burden group animals. The animals were sacrificed on the day of exposure to ^{14}C-HMDS (day 1 or 15).

c. Body Burden (Groups 3 and 9)

This group was used to determine the total amount of radioactivity remaining in the animal immediately following the ^{14}C-HMDS exposure period. These results were used for comparison to the excreta animals for determination of percents of administered dose. These animals were sacrificed while on the chamber and no earlier than 10 minutes before the end of the ^{14}C-HMDS exposure (day 1 or 15).

d. Tissue Distribution (Groups 4 and 10)

This group was used to evaluate tissue disposition and kinetics of both parent HMDS and total radioactivity following a single and repeated nose-only vapor

inhalation exposures to 5000 ppm of HMDS. Four animals were sacrificed at each terminal time point.

e. Excreta (Groups 5 and 11)

This group was used to determine the elimination pathway of the test article. The amount of radioactivity in each of the possible elimination routes was directly compared as a fraction of the total amount of radioactivity found. In addition, the amount of radioactivity in each route was compared as a percent of the radioactivity found in the body burden group post ^{14}C-HMDS exposure (day 1 or 15).

f. Body Burden Spares (Groups 6 and 12)

This group was used to replace any animals with non-patent cannulas in the body burden group before or during the ^{14}C-HMDS exposures. Animals not used in this group were sacrificed and discarded after the exposure.

3. Test Article Preparation and Analysis

a. Preparation:

Unlabeled HMDS was used as supplied. Radioactive dosing solution was prepared by adding an appropriate volume of unlabeled HMDS to the ^{14}C-HMDS, until a target specific activity, sufficient to deliver 50 to 80 μCi to each animal, was achieved. This dosing solution was prepared and analyzed three days prior to use.

b. Analysis:

A verification of the dosing solutions radiochemical purity was evaluated on the day of preparation using HPLC with radiochemical detection. The purity was verified to be 99.28% on the day of preparation for the repeat exposure and 99.40% for the single exposure. **Figure 1** provides a representative chromatogram from the radiochemical purity evaluations. Specific activity of the dosing solution was performed by liquid scintillation analysis on the day of preparation as well as prior to use on the day of use for both the repeat and single exposures. The specific activities

performed on these separate days did not differ by more than a 10% relative range and the dosing solution was considered acceptable for use.

4. Test Article Administration

The route of the test article administration for the repeat exposure was nose-only inhalation, six-hours/day, for fifteen consecutive days, to an air atmosphere containing a target HMDS concentration of 5000 ppm (days 1-14) and 5000 ppm ^{14}C-HMDS (day-15 only) vapor. The route of test article administration for the single exposure was nose-only inhalation, six hours/day, for one day, to an air atmosphere containing a target HMDS concentration of 5000 ppm ^{14}C-HMDS vapor. Nose-only vapor inhalation was selected as the route of exposure to stay consistent with previous pharmacokinetic, biochemical and reproductive studies in which inhalation was the route.

5. Exposure Duration and Schedule of Events

Before initiation of the repeat or single exposure period, animals were transferred into individual restraint cones (exposure cones) designed for attachment to the Cannon style nose-only system. Animals were acclimated to these exposure cones for four consecutive days prior to initiation of the exposure. Acclimation periods were approximately one, two, four and six hours; respectively.

a. Unlabeled HMDS Repeat (Days 1-14) Exposure

Each animal, with the exception of the control animals, was exposed to unlabeled HMDS for six hours a day, 7 days a week, for 14 consecutive days. Each animal was individually positioned in a plastic restraint cone for direct attachment to the nose-only exposure chamber. Prior to attaching the restraint cone, the exposure chamber was started and operating near the target concentration (±10%). The exposure start time for an individual animal was defined as the time of attachment of the restraint cone, containing the animal, onto the chamber. Upon completion of daily exposures, the animals were removed from the cone and returned to their appropriate housing cages.

b. Labeled HMDS Repeat (Day 15) and Single Exposures

Each animal, with the exception of the control animals, was exposed to ^{14}C-HMDS for six consecutive hours on exposure day 15 of the repeat exposure and on the day of the

single exposure. Cannulated animals were positioned such that the cannula was easily accessible for blood collection without interrupting the exposure. The exposure start time for an individual animal was defined as the time of attachment of the restraint cone, containing the animal, onto the chamber. For the exposure period, individual animal start times were staggered by approximately two minutes. During the exposure, blood collections were made from animals in groups 4 and 10. Blood collection during the exposure occurred at the 3-hour time point following initiation of the exposure. Following six consecutive hours of exposure, the animals in the body burden groups 3 and 9 were euthanized while on the exposure chamber and the cones containing animals were removed from the chamber. The exposure completion time was defined as the time of euthanasia for the body burden animals and time of removal from the exposure chamber for all remaining animals.

6. Observations

a. Mortality/Morbidity/Daily Observations

All animals were observed in their cages for mortality, morbidity, and signs of distress once daily through the completion of the in-life phase of the study.

b. Body Weight Measurements

Individual body weights were measured and recorded for each animal on the day of randomization, prior to exposure start on day 1, day 15, and prior to euthanasia. The body weights obtained prior to exposure day 15 and day 1 were used for the body burden animals.

7. Sample Collections

Methods of Euthanasia/Terminal Procedures

(Groups 1, 4, 5, 7, 10 and 11)

Animals were anesthetized using 15% isoflurane in mineral oil. Anesthetizing chambers were prepared by saturating gauze placed in the bottom of 250 mL beakers with the 15% isoflurane mixture, and a latex glove was stretched over the top to eliminate evaporation. The animal was anesthetized by inserting its nose into a hole through the glove covering the beaker containing the 15% isoflurane mixture. Once they reached a deep surgical plane they were exsanguinated via open thoracic cardiac puncture.

(Groups 2, 3, 8 and 9)

Animals were euthanized by intravenous injection of Euthasol® CIII through the jugular cannula.

(Groups 6 and 12)

Animals were euthanized by CO_2 asphyxiation until respiration ceased.

a. Body Burden (Groups 3 and 9)

While loaded onto the exposure chamber, animals were euthanized no earlier than ten minutes prior to completion of the ^{14}C-HMDS exposures using an overdose injection of Euthasol® CIII through the jugular cannula. Following euthanasia, the animals were immediately removed from the restraint tube and the entire carcass placed into a pre-weighed digestion flask containing 35% tetraethyl ammonium hydroxide (TEAH). Urine and feces voided during the exposure was collected in the same digestion flask. Following removal of the carcass, each restraint tube was rinsed with 35% TEAH. This rinse was collected directly into the digestion flask containing the carcass with the carcass and rinse digested *in toto* to determine the body burden of radioactivity immediately following the ^{14}C-HMDS exposures.

b. Tissue Distribution (Groups 4 and 10)

The samples collected for the blood and tissue distribution animals are outlined in **Table I**.

Blood

On the day of the ^{14}C-HMDS exposures, blood was drawn at the 3 hour time points during the exposure period from animals in groups 4 and 10. Animals were removed from the chamber and blood was collected by cardiac puncture either by using a

heparinized syringe equipped with a 23 gauge needle or heparinized vacutainer. Following the exposures, blood was collected by cardiac puncture in groups 4 and 10 at 0 hr (5 min), 10, 30 minutes, 1, 2, 12, 24, 72, 120 hours. To complete the blood kinetics time points, collections were also made via cardiac puncture from groups 5 and 11 animals at the 168-hour post ^{14}C-HMDS exposure interval. During blood collections an aliquot of blood 100 - 200µL was collected and immediately transferred into a glass vial containing internal standard spiked in Tetrahydrofuran (ISTD/THF) containing glass beads and extracted according to the method "Procedure for Determination of HMDS in Biological Matrices (Blood and Tissues)" **Appendix C**, for analysis of parent HMDS concentrations by gas chromatography-mass spectrometry (GC/MSD). Also, duplicate aliquots of whole blood were analyzed for total radioactivity by liquid scintillation counting (LSC).

Tissues

At terminal sacrifice points (0, 2, 12, 24, 72 and 120 hour post exposure), brain, kidneys, testes, liver, lung, and a portion of peri-renal fat were harvested as follows. The animals were anesthetized as described above and exsanguinated via open thoracic cardiac puncture. As quickly as possible following collection of blood, the brain, kidneys, testes, liver, lung and a portion of peri-renal fat were removed, dissected free of fat (if applicable), blotted of excess blood and placed into pre-weighed containers. The collected tissues were placed on ice until all samples were collected for that time point at which time the samples were processed immediately. The tissue samples were extracted with THF and an aliquot of each extract was analyzed by GC/MSD according to the method "Procedure for Determination of HMDS in Biological Matrices (Blood and Tissues)" **Appendix C**. Also, an aliquot of the extracts was analyzed by LSC for radioactivity content. Additionally the extracted pellet was solubilized using TEAH; the weight of the pellet and TEAH was obtained.

Between each tissue, surgical instruments were rinsed with 70% ethanol followed with water filtered by reverse osmosis (RO). Carcasses were discarded following tissue collections.

c. Excreta (Groups 5 and 11)

A total of six Roth-style glass metabolism cages (five for excreta groups and one for control groups) designed for rats, were used for this study. Each cage was set up and operated at target flow rates and conditions for a minimum of 48 hours prior to housing animals. During this time the system was evaluated for leaks. Room air was drawn through the cages using a vacuum pump. The airflow rate through each cage was monitored using a flow meter and was maintained between 0.5-1.0 LPM. This flow-rate was recorded a minimum of twice per day. The room air entering the system passed though a series of Drierite® and Ascerite® canisters designed to remove H_2O and CO_2 respectively. The temperature within the cage was monitored and recorded at least once in the A.M. and in the P.M. every day during which an animal was housed in the cage.

The sample collections for Groups 5 and 11 are provided below:

Excreta

Groups	Urine and Feces Collection Times (Hours post-exposure)	$^{14}CO_2$ Collection Times (Hours post-exposure)	Expired Volatile Collection Times (Hours post-exposure)
5 and 11	6, 12, 24, 48, 72, 96, 120, 144, 168*	24, 48, 72, 96, 120, 144, 168*	1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, 168*

* = Terminal Sacrifice. Blood, tissues, and carcass were collected and processed for analysis.

Urine

Roth-style glass metabolism cages modified to allow direct collection of urine into 4 oz. glass jars were used. Jars were labeled and pre-weighed prior to attachment to the cage. Each jar was maintained on dry ice during all collection intervals. At the appropriate time point, jars were removed from the cage, capped and maintained on dry ice or placed in an -80°C freezer until processing for radioactivity analysis by LSC. Prior to processing, each jar was re-weighed to determine the sample weight. In addition, when

sufficient radioactivity was present in the urine samples (> 25,000 dpm/ml); a metabolic profile was obtained using HPLC with radiometric detection.

Feces

Roth-style glass metabolism cages modified to allow direct collection of feces into 4 oz. glass jars were used. Each jar was labeled and pre-weighed prior to attachment to the cage. Each jar was maintained on dry ice during the collection interval. At the appropriate time point, the jars were removed from the cage, capped and maintained on dry ice or placed in an -80°C freezer until processing. Prior to processing, each jar was re-weighed to determine the sample weight. Feces samples were diluted with Milli-Q water (3:1 w/v) and then homogenized. Following the homogenization, aliquots were solubilized using 35% TEAH followed by analysis by LSC for radioactivity content.

Expired Volatiles

Glass charcoal tubes were placed in line on the outlet side of the cage and were used for trapping expired volatiles. One tube was used per cage, per collection interval. Each tube was scored and opened at each end prior to attachment. At the appropriate time point, the charcoal tube was removed, capped, and transferred to the cold room (5 ± 4°C) for storage and processing.

While in the cold room, the charcoal tubes were uncapped and the contents dumped into pre-weighed vials containing hexane. The contents of the tubes were then desorbed with hexane. Aliquots of the hexane were taken for parent HMDS analysis by GC/MSD according to the method "Procedure for Determination of HMDS in Expired Volatiles (Charcoal Tubes)" **Appendix C** and duplicate aliquots were removed for total radioactivity analysis by LSC.

Carbon Dioxide (CO_2)

Cage exhaust air after passing through charcoal tubes was drawn through a glass gas trap containing 4N potassium hydroxide (KOH). Each gas trap was filled prior to initiation of the collection interval. At the appropriate collection interval, KOH was collected into pre-weighed 8 oz. glass jars, capped, and transferred to the cold room (5 ± 4°C) for

storage and processing. Aliquots of the KOH were taken and analyzed by LSC for radioactivity.

Carcass and Tissues

At the terminal sacrifice time point (168 hour post exposure) excreta animals were removed from the metabolism cage, the animals were anesthetized using isoflurane as described above and exsanguinated via cardiac puncture. A maximum volume of blood possible was collected to ensure euthanasia of animal. Blood was processed immediately. As quickly as possible following collection of blood, the brain, kidneys, testes, liver, lung and a portion of peri-renal fat were removed, dissected free of fat (if applicable), blotted of excess blood and placed into pre-weighed containers. The collected tissues were placed on ice until all samples were collected for that time point at which time the samples were processed immediately for parent and radioactivity analysis. After removal of tissues, each residual carcass was immediately placed into a pre-weighed jar containing 35% TEAH for solubilization *in toto*. The carcass was kept at room temperature until completely solubilized and analyzed for radioactivity content by LSC.

Metabolism Cages (Cage Rinse)

Following removal of the animals at the 168-hour collection interval, the glass metabolism cages were rinsed with THF followed by hexane. The rinse was collected in pre-weighed jars and stored in the cold room (5 ± 4°C) until analysis. An aliquot of each cage rinse was taken and analyzed by LSC for radioactivity.

8. Controls

Tissue Distribution/Excreta Controls (Groups 1 and 7)

Group 1 and 7 control animals were placed into metabolism cages and then treated the same as the excreta group (Group 5 and 11). Urine, feces, expired volatiles and CO_2 were collected from these animals up to the time of euthanasia. The 24-hour post exposure samples were processed the same as the excreta group and served as analytical controls. All other samples collected from these animals were discarded. The animals were sacrificed as close as possible to the 168-hour post exposure time point. Blood and

tissues were collected and processed in the same manner as described for the tissue distribution group animals and served as analytical control samples.

Body Burden Controls (Groups 2 and 8)

Following euthanasia via an overdose injection of Euthasol® CIII, these rats were removed from the restraint tubes. The carcasses were placed into a pre-weighed digestion flask containing TEAH. An aliquot of the solubilized carcasses was taken and analyzed by liquid scintillation analysis and the total radioactivity determined. These values served as background for Group 3 and 9 animals.

9. Sample Analysis

Radioactivity Measurements

Radioactivity analysis was conducted using a Packard Model 2500TR and 3100TR LSC. Each sample was counted for at least 5 minutes or a 2 sigma error of 2%, whichever came first. Tissues were extracted with THF containing internal standard. Following the addition of THF, the tissues were cut into small pieces to improve surface area. Duplicate aliquots of the extract were removed, weighed and added to liquid scintillation cocktail for radioactivity measurement. After extraction, the tissue residues remaining were solubilized using 35% TEAH and duplicate aliquots were removed and placed into liquid scintillation cocktail for radioactivity measurement. Feces were homogenized with Milli-Q water (~3:1 water:feces). Duplicate aliquots were removed, weighed, and solubilized with 35% TEAH. Following digestion, samples were neutralized with 30% H_2O_2. Liquid scintillation cocktail was added and radioactivity was measured. Whole blood was solubilized using Soluene 350:Isopropanol (1:1) or 35% TEAH. Duplicate aliquots of the digested blood were removed and placed into liquid scintillation cocktail for radioactivity measurement. Radioactivity collected by the charcoal tubes was extracted with hexane and duplicate aliquots of the extract were added to liquid scintillation cocktail and radioactivity was measured. Urine and KOH samples were added directly to liquid scintillation cocktail for radioactivity measurement. Carcass samples were digested in appropriate volumes of 35% TEAH. Following digestion,

duplicate aliquots were removed, weighed, and neutralized with HCl. Liquid scintillation cocktail was then added and radioactivity was measured.

Parent HMDS Analysis

Aliquots of blood and tissues were extracted with THF according to the validated method (Durham 2004). Parent HMDS was quantitated in the THF extracts of blood and tissues against THF solvent standards using gas chromatography with mass selective detection (GC/MSD) according to the validated method "Procedure for Determination on HMDS in Biological Matrices (Blood and Tissues)"**Appendix C**. Charcoal tubes were desorbed with hexane according to the validated method (Durham 2004). Parent HMDS was quantitated in a similar manner against hexane standards using GC/MSD according to the validated method "Procedure for Determination on HMDS in Expired Volatiles (Charcoal Tubes)" **Appendix C**.

10. Data Analysis

Numerical data obtained during the conduct of this study were subjected to calculations of group mean values and standard deviations, where appropriate.

Body Burden

The percentage of radioactivity retained was calculated for each animal in the body burden group by dividing the total radioactivity measured in each animal by the calculated achieved ^{14}C dose. The calculated achieved ^{14}C dose was calculated as follows:

$A = \frac{(B \times C)}{1000} \times D \times E$ where:

A = Achieved ^{14}C Dose (dpm)

B = respiratory minute volume (V_E, ml/min) calculated on the basis of body weight: $\{V_E = 2.1 (BW \text{ grams})^{0.75}\}$

C = exposure duration (minutes)

D = achieved mean ^{14}C-HMDS vapor concentration (mg/L)

E = calculated specific activity of the ^{14}C-HMDS dosing solution (dpm/mg)

1000 = conversion of milliliters to liters

Tissue Distribution

Parent HMDS and total radioactivity was measured in blood and tissues. The concentration of radioactivity in whole blood and tissues was recorded in dpm/g tissue and μg ^{14}C-HMDS equivalents per gram sample. The calculation of ^{14}C-HMDS equivalents was based upon the specific activity of the dosing solution. The concentration of HMDS in whole blood and tissues was reported as μg HMDS/g sample.

Excreta

Parent HMDS and total radioactivity was measured in the expired volatile samples (charcoal tubes) as described above. For urine, feces and expired $^{14}CO_2$ samples total radioactivity was determined as described above. The radioactivity content in the excreta was reported both in terms of percent of total radioactivity recovered relative to the amount of radioactivity in the body burden group and normalized to the mean total radioactivity recovered in the excreta group. The rate of radioactivity excretion was reported in terms of μg ^{14}C-HMDS equivalents/hr. In urine samples with >25,000 dpm/ml, an aliquot of urine was analyzed by HPLC with radiometric detection to obtain a metabolic profile.

Controls

These samples served to determine background levels for parent and radioactivity analysis.

Statistical Measures

All statistical analyses were conducted using SAS version 9.13. Areas under the curve (AUCs) were calculated for both radiolabeled and parent compound using Bailer's method which produces both a mean and a standard error. These statistics were used to calculate upper and lower confidence limits on the AUCs. Comparisons between the parent and radiolabeled compound AUCs in the charcoal tubes, blood, lung, liver, kidney, brain, testes, and fat were done using the values from the Bailer method (Nedelman et al., 1995) and the Satterthwaite (Nedelman and Jia, 1998) approximation method. Statistical analyses are presented in **Appendix D**.

11. Deviations

a. Control excreta animal for single exposure was sacrificed after the animals in the excreta group. This deviation did not impact this study due to each cage being independently controlled for airflow.

b. Parent HMDS sample processing was changed to eliminate centrifuging from extraction process. Centrifuging was not required to achieve separation. QC spikes were always analyzed in the same manner alongside the study samples to ensure extraction efficiency. This did not impact the study.

c. During the 6 hour collection for the repeat exposure the urine and feces samples were not collected. The 6 hour time point will not be available for urine and feces time course evaluations. This did not impact the outcome of the study.

d. Chamber conditions were not recorded at 30-minute intervals on five occasions. The largest gap in recording was 37 minutes. This did not impact the outcome of the study.

e. The protocol stated a 100 mL beaker would be used for anesthetizing the animals. A 250 mL beaker was used instead for ease of handling. This did not impact the outcome of the study.

f. The protocol stated the j-tube would be heated and maintained at 90-110° C. During one observation the j-tube temperature was recorded to be 112° C. This did not impact the outcome of the study.

g. The protocol stated that the randomization would occur on study day -4 for the single exposure. The randomization was actually conducted on study day -5. This did not impact the outcome of the study.

h. The recorded percent relative humidity (%RH) was outside the protocol specified range (30-70%) on two occasions for an animal room. These variations occurred over very short periods of time and were considered not to have an impact on the study.

i. The room air changes per hour for animal rooms 196A and 196B were outside the protocol specified range of 10-15 air changes per hour. 196A was measured to be 16.4 air changes per hour and 196B was measured to be 17.2 air changes per hour. This did not impact the outcome of the study.

j. The protocol stated Soluene 350:Isopropanol (1:1) would be used to solubilize whole blood for radioactivity analysis. TEAH instead of Soluene 350 was used to solubilize during the single exposure. This did not impact the outcome of the study.

III. RESULTS

Nose-only vapor inhalation single exposure was conducted by a single six hour exposure to ^{14}C-HMDS. The repeat exposures were conducted for six hours/day, seven days/week for fourteen consecutive days to unlabeled HMDS followed by a single six-hour exposure to ^{14}C-HMDS on day fifteen. Organization of group assignments is provided in **Table I.**

A. INHALATION EXPOSURES

1. Pre-Exposure Evaluations

a. Verification of Test Article Vapor Generation

Prior to initiating exposures, test runs demonstrated that test article concentrations within 10% of the targeted 5000 ppm of HMDS could be obtained while maintaining an actual to nominal percent difference in concentration of ≤10%. The correlation of actual and nominal concentrations (≤10%) demonstrated that the test article was in a vapor state.

b. Homogeneity of Test Article Atmosphere within Exposure Chamber

Prior to initiation of the exposure period, an evaluation of the test article atmosphere homogeneity within the exposure chamber was conducted. During this evaluation the chamber was operated within normal operating parameters. The chamber temperature and humidity was 22.2°C and 28.6 %RH, respectively. The mean measured chamber airflow was 28.1 liters per minute. During the evaluation, a total of three samples were collected at each of the seven levels. The average of the three replicates was determined and compared to the calculated nominal chamber concentration during the homogeneity evaluation. All levels demonstrated a percent difference of average port concentration to calculated nominal

concentration within the acceptable 10% range. The results of this evaluation are summarized and presented in **Table II**.

c. Evaluation of Percent Oxygen during Exposure

Prior to initiation of the exposure period, the percent of oxygen was measured from three levels of the exposure chamber. The measured oxygen content was 20.7 % as measured with a Bacharach model Oxor® II oxygen monitor and is presented in **Table II**. During this evaluation, the chamber was operating at a mean airflow of 28.1 LPM, temperature of 22.2°C and a humidity of 28.6 %RH. The mean measured concentration of HMDS within the chamber during this evaluation was 4978 ± 48.8 ppm with a calculated nominal concentration of 4944 ppm.

2. Environmental Conditions during Single and Repeat Exposures

During the single 6 hour exposure, the average daily mean temperature, relative humidity and airflow within the chamber was 23.2 ± 0.56 °C, 28.2 ± 1.80% and 28.0 ± 0.00 liters per minute, respectively. During the fifteen days of repeat exposure, the average daily mean temperature, relative humidity and airflow within the chamber was 22.8 ± 0.67 °C, 26.2 ± 2.05% and 28.1 ± 0.04 liters per minute, respectively. The chamber environmental conditions during each exposure are summarized in **Table III**. Individual data from each exposure are presented in **Appendix A**.

3. Test Article Concentration during Exposures

Measured and calculated nominal chamber concentrations during each exposure period are summarized in **Table IV.**

a. Measured Chamber Concentration

During the single exposure the mean measured daily chamber concentration averaged 4989 ± 189.6 ppm. During repeat exposure the mean measured daily chamber concentrations ranged from 4833 to 5365 ppm over the fifteen days of exposure with an average of 4999 ± 98.0 ppm for exposure days 1 through 14 and 5365 ± 66.6 ppm on exposure day 15. **Figure 2** provides a representative chromatogram of the on-line chamber analysis during an exposure period with

Figure 3 providing a graphical representation of the mean daily measured concentrations for each exposure period. Individual measured chamber concentrations for each exposure are presented in **Appendix B**.

b. Calculated Nominal Chamber Concentration

For the single exposure the calculated nominal concentration was 5130 ppm. For the repeat exposure the calculated nominal concentrations ranged from 4802 to 5143 ppm over the fifteen days of exposure with an average of 4970 ppm. Concentrations were determined using the amount of test article used and the total volume of air that passed through the system during the exposure period. The measured vs. nominal percent ratios calculated were 97.2% for the single exposure and ranged from 97.0% to 105.0% over the 15 repeat exposures.

B. DISPOSITION OF PARENT AND ^{14}C-HMDS

1. Body Burden

Total radioactivity was measured in the carcass and exposure cone rinses upon immediate removal from the exposure chamber following day 15 of the repeated exposure and day 1 of the single exposure. The percentage of radioactivity retained was calculated for each animal in the body burden group by dividing the total radioactivity measured in each animal by the calculated achieved ^{14}C dose. These results are summarized and presented in **Table V**.

The targeted dose of radioactivity (^{14}C) during the six-hour exposure interval on day one of the single exposure and day fifteen of the repeat exposure was 50 - 80 µCi/rat at a target chamber vapor concentration of 5000 ppm HMDS.

For the single exposure the mean measured chamber concentration during the ^{14}C-HMDS exposure interval, presented in **Table IV,** was 4989 ± 189.6 ppm (32.9 ± 1.25 mg/L) as measured using on-line GC analysis. Using this mean measured chamber concentration, the calculated specific activity of the ^{14}C-HMDS solution (0.048 mCi/g) and the respiratory minute volume (2.1 x body weight (g)$^{0.75}$), the average calculated achieved

^{14}C-HMDS dose during the single six-hour interval (mean ± S.D.) was 66.5 ± 1.73 μCi (147622156 ± 3851609.0 dpm).

For the repeat exposure the mean measured chamber concentration during the ^{14}C-HMDS exposure, presented in **Table IV**, was 5365 ± 66.6 ppm (35.3 ± 0.44 mg/L) as measured using on-line GC analysis. Using this mean measured chamber concentration, the calculated specific activity of the ^{14}C-HMDS solution (0.055 mCi/g) and the respiratory minute volume (2.1 x body weight (g)$^{0.75}$), the average calculated achieved ^{14}C-HMDS dose during the single six-hour interval (mean ± S.D.) was 82.0 ± 2.78 μCi (182135609 ± 6171785.4 dpm).

The total body burden of radioactivity measured in the male Fischer 344 rats during the single exposure ranged from 4913295 to 5993004 dpm with a mean value of 5369562 ± 460232.7 dpm. The total body burden of radioactivity measured during the repeat exposure ranged from 5484513 to 8629135 dpm with a mean value (mean ± S.D) of 6979556 ± 1502820.3 dpm. These animals were injected with Euthasol® CIII euthanasia solution, no earlier than ten minutes prior to completion of the ^{14}C-HMDS exposure. During the euthanasia process the animals remained loaded in the cone and attached to the exposure chamber, while exposed to test article, until respiration could not be detected. Based on the mean body burdens and the calculated dose, the percent of the total radioactive dose which was retained during the six-hour exposure (mean ± SEM) was 3.6% ± 0.24 for the single exposure and 3.8% ± 0.86 for the repeat exposure. This body burden measurement is reflective of the animal's ability to extract HMDS from the air during the exposure and this extraction efficiency is highly dependent on systemic metabolism. Body burden data are presented in **Appendix C** with summarized results in **Table V.**

2. Tissue Distribution

Following single or repeated exposures, parent HMDS and total radioactivity were measured in the blood, and selected tissues (brain, kidneys, testes, liver, lung and perirenal fat). The concentration of parent HMDS in whole blood, and selected tissues are reported as μg HMDS/g sample. The total radioactivity ^{14}C-HMDS concentrations in

whole blood and tissues were recorded in μg equivalents HMDS/g sample (μg Eq. HMDS/g). The calculation of ^{14}C-HMDS equivalents was based upon the specific activity of the dosing solution used during the exposure period. The concentrations in blood, brain, kidneys, testes, liver, lung and fat are presented as group means with standard errors of the means (SEM) in **Tables VI** through **XII**. The corresponding individual animal values for these parameters are presented in **Appendix C.**

Following single or repeated exposures, radioactivity was distributed to the tissues with the highest concentrations found in fat, kidney and liver. Concentrations of radioactivity in the blood with time were consistently lower than for the other tissues. Radioactivity in tissues and blood was measurable through 168 h in blood and tissues following single and repeated exposure. Following single and repeated exposures, parent HMDS was detected in all tissues with the highest concentrations in all tissues at 0 h post-exposure except fat during the repeated exposure which had the highest concentration of parent HMDS at 2 h post-exposure. In blood the concentration of parent HMDS was at lower levels than in the other tissues. Parent HMDS was measurable in brain, kidney, testes, liver and fat through 168 h post-exposure. In blood parent HMDS was detected through 24 h post-exposure and in lung tissue through 72 h for single exposure and 168 h for repeat exposure.

Calculation of the area under the curves (AUC) for ^{14}C-HMDS as well as parent HMDS in blood, brain, kidneys, testes, liver, lung and fat following single and repeated exposures are presented in **Table XV.** Graphical presentations of the ^{14}C-HMDS and parent HMDS concentrations in each of the matrices are presented in **Figures 4-10.** Additional disposition kinetic parameters for total ^{14}C-HMDS and parent HMDS, time to maximum concentration (T_{max}), maximum concentration (C_{max}), and terminal half-life of elimination ($t_{1/2}$), are presented in **Table XVI.**

As the AUC for total radioactivity is composed of both ^{14}C-HMDS and labeled metabolites, comparison to the AUC derived from parent HMDS, demonstrates the percentage of the ^{14}C-pool that is composed of metabolites. All tissues had measurable

concentrations of both parent HMDS and metabolites. Following the single exposure, the percentage of the total radioactivity attributed to metabolites ranged from 61.37% to 98.35%; liver (98.35%), blood (94.69%), brain (88.35%), lung (84.99%), testes (66.64%), and kidney (61.37%). In fat approximately 17% was attributed to metabolites following the single exposure. Following repeated exposures, the percentage of the total radioactivity attributed to metabolites in the tissues ranged from 38.12% to 97.49%; liver (97.49%), blood (97.09%), brain (89.04%), lung (77.48%), testes (55.66%), and kidney (38.12%). The percentage of radioactivity as parent HMDS detected in fat following a single exposure was ~83 % and that in kidney was ~39%, in testes ~33% and in lung tissue 15%. Following repeated exposure the percentage of total radioactivity attributed to parent HMDS increased to ~62% in kidney, increased to ~44% in testes and increased to ~23% in lung tissue.

The percentage of radioactivity as metabolites in fat tissue following repeated exposures could not be determined. The AUC for parent HMDS in the repeated exposure group may represent residual HMDS from the previous 14 days of HMDS exposure in addition to the ^{14}C-HMDS from the 15th day of exposure. This residual amount depends on the rate of clearance during the 24 h period between exposures. Since the calculated AUC for parent HMDS was higher than the AUC for radioactivity, this residual contribution did not allow for calculation of the percentage of the total radioactivity attributed to metabolites in fat tissue.

While the AUC of total radioactivity in testes was higher than the AUC of parent HMDS in testes, the average concentration of parent HMDS in the testes was higher at time 0 following the single exposure. This is not possible for a single exposure where the only exposure was radiolabelled and any parent HMDS would be due to this radiolabelled exposure unlike as previously described for fat following repeated exposures. An explanation for this observation is that the parent HMDS concentrations are corrected for any potential sample processing loss (extraction efficiency and solubilization efficiency) by the use of the internal standard method. Neither the extract radioactivity analyses nor the tissue pellet radioactivity analyses are corrected for sample processing efficiencies.

The individual tissue absolute extraction efficiencies (based on radioactivity without internal standard correction) are presented in **Appendix C.** The absolute extraction efficiencies for the testes collected after the single exposure were significantly lower (~17% compared to ~80%) than all other tissues (including testes from repeated exposures) when comparing samples collected at 0 hour. It is possible that a greater loss of radioactivity occurred in sample processing with this tissue following the single exposure resulting in an underestimation of the total radioactivity in testes from a single exposure.

Statistical analyses were conducted comparing the calculated AUCs for the single vs the repeated exposures for both parent HMDS and radioactivity **(Appendix D).** When comparing the AUCs for parent HMDS between single and repeated exposures, statistical significance was demonstrated between the single and the repeated exposures for the following tissues: fat, kidney, and testes. A statistical difference was also calculated for AUCs based on radioactivity between the single and repeated exposure groups for blood, brain, fat, kidney, lung, and testes.

In both the single and repeated exposure groups, tissue to blood AUC ratios were greater than 1 for all tissues. The lowest tissue to blood ratios were observed in liver following both the single and repeated exposures. The highest tissue to blood AUC ratios were observed in kidney and fat following both single and repeated exposures. The ratio of the AUC for HMDS in kidney to the AUC for HMDS in blood was 74 and the tissue to blood ratio for fat was 2244 in the repeated exposure group. Comparison of the parent HMDS AUCs tissue to blood ratios from the single and repeated exposures, show that in all cases the repeat exposure was higher than the single exposure. These ratios for kidney, liver and fat were about 2-fold higher than the tissue to blood ratios in the single exposure group. The tissue to blood ratios for brain and lung were similar between the single and repeated exposure groups. The tissue to blood ratio for testes was ~3-fold higher following repeated exposure as compared to the ratio calculated for the single exposure group.

3. Kinetic Analyses

Pharmacokinetic parameters for radioactivity and parent HMDS were calculated for animals exposed to single and repeated exposures of HMDS **(Table XVI, Figures 4-10)**. For blood and tissues the highest concentration of radioactivity (Cmax) was measured at 0 or 2 hours post-exposure (T_{max}). The highest radioactivity concentrations at Tmax were observed in fat and kidney. Similarly, for blood and tissues the highest concentration of parent HMDS was observed at 0 or 2 hours post-exposure with the highest parent HMDS concentrations measured in fat and kidney following the single exposure and in fat and liver after the repeated exposures.

Elimination half-lives for radioactivity and parent HMDS were similar between the single exposure and the repeated exposure groups. Elimination of radioactivity from blood and tissues other than fat was multi-phasic, with the majority of the radioactivity eliminated within 24 h post-exposure. The terminal half-life for elimination of radioactivity from blood was ~36 h and 39 h for the single and repeated exposures, respectively, and parent HMDS in blood was detected only through 24 h post-exposure. Terminal half-lives of elimination for radioactivity of over 40 h were measured in liver, lung and testes after the single exposure and in liver, lung, testes, and brain after repeated exposures. In general, half-lives of elimination were 1 to 3 fold faster for parent HMDS than radioactivity; notable was the faster elimination half-life of HMDS from lung tissue. In addition blood parent HMDS levels were not measurable beyond 24 h post-exposure.

4. Mass Balance

The mass balance of radioactivity is presented for each exposure as a percent of the body burden dose ± SEM and as a percent of total recovered dose ± SEM in **Table XVII.** The overall mass balance of radioactivity, as a percent of the body burden dose, ranged from 107.4% to 121.8% (mean ± SD, 114.0% ± 5.6) for the single exposure and 120.0% to 133.7% (mean ± SD, 128.4% ± 5.5) for the repeat exposure. Individual data are presented in **Appendix C** with a graphical representation of the overall recovery presented in **Figures 16** and **17** as the percent of body burden dose and percent of the

total recovered dose for the single and repeat exposures, respectively. The majority of the radioactivity (~80%) was eliminated by 24 h post-exposure.

An equal percentage, 46%, of the recovered dose was excreted in urine and in expired volatiles following the single exposure **(Figure 17).** Following the repeat exposure the percentage of recovered dose in the urine increased to 64% with a corresponding decrease in expired volatiles (28%). Fecal elimination was ~2% for the single and repeated exposures. Collected tissues accounted for less than 0.2% of the recovered dose and radioactivity remaining in the carcass was ~ 3% of the recovered dose for both the single and repeated exposures. Following sacrifice at the 168-hour post exposure time point, brain, kidneys, testes, liver, lung and a sample of perirenal fat were collected and processed for radioactivity. The percent of radioactivity remaining in these tissues (sum of the mean values), relative to the recovered dose, was 0.20% and 0.13% for single and repeat exposures, respectively. Radioactivity measured in the remainder of the carcasses, comprised mainly of muscle, bone and fat, accounted for 3.8 % and 2.7% of the recovered dose for single and repeat exposures respectively. Results of the mass balance are summarized in **Table XVII**.

5. Elimination

Following day one of the single exposure and day fifteen of repeated exposures parent HMDS and total radioactivity concentrations were measured in expired volatiles. The concentration of parent HMDS in expired volatiles was reported as μg HMDS/h. The total radioactivity ^{14}C-HMDS concentrations in expired volatiles and expired CO_2 were recorded in μg equivalents HMDS/h. The total radioactivity ^{14}C-HMDS concentrations in urine and feces were recorded in μg equivalents HMDS/g sample. The calculation of ^{14}C-HMDS equivalents was based upon the specific activity of the dosing solution used during the exposure period. The concentrations in expired volatiles, urine, feces and expired CO_2 are presented as group means with standard errors of the means (SEM) in **Tables XIII** and **XIV**. The corresponding individual animal values for these parameters are presented in **Appendix C.**

Parent HMDS and radioactivity concentrations in expired volatiles were measurable following single and repeated exposures through 168 h post-exposure. The highest concentrations were measured in the first collection interval and decreased by approximately one half by the second collection interval. Notable is the constant ratio of HMDS to radioactivity in each of the collection intervals, ~47%, following the single exposure. The amount of parent HMDS measured in the expired volatiles following the repeated exposure is higher than the radioactivity measured due to elimination of residual parent HMDS from the 14 days of non-radiolabeled HMDS exposures. This is likely due to elimination from the fat deposits.

Concentrations of radioactivity were measurable in urine, feces and as $^{14}CO_2$ following the single and repeated exposures through 168 h post-exposure with the highest concentrations found at each interval in urine.

An AUC analysis for expired volatiles is presented in **Table XV.** Following a single exposure, approximately 53% of the total radioactivity in expired volatiles was attributed to metabolites. Graphical presentations of ^{14}C-HMDS and parent HMDS concentrations in expired volatiles and of radioactivity in urine, feces and as CO_2 are presented in **Figures 11-14.** Additional disposition kinetic parameters for total ^{14}C-HMDS and/or parent HMDS in expired volatiles, feces, urine and CO_2 (t_{max}, C_{max}, and $t_{1/2}$) are presented in **Table XVI.** The maximum concentration of radioactivity found in expired volatiles [illegible] the first 0-[illegible] collection interval following the single and repeated exposures. Following a single exposure the maximum concentration of radioactivity in feces was found in the 12-24 h post-exposure interval and in the 6-12 h post-exposure interval in urine). The highest concentration of $^{14}CO_2$ [illegible] 0-24 h post-[illegible] [illegible] feces, urine and CO_2 between the single (range of 16-22 h) and repeated (range of 25-[illegible] h) exposure groups.

Parent HMDS and radioactivity concentrations in expired volatiles were measurable following single and repeated exposures through 168 h post-exposure. The highest concentrations were measured in the first collection interval and decreased by approximately one half by the second collection interval. Notable is the constant ratio of HMDS to radioactivity in each of the collection intervals, ~47%, following the single exposure. The amount of parent HMDS measured in the expired volatiles following the repeated exposure is higher than the radioactivity measured due to elimination of residual parent HMDS from the 14 days of non-radiolabeled HMDS exposures. This is likely due to elimination from the fat deposits.

Concentrations of radioactivity were measurable in urine, feces and as $^{14}CO_2$ following the single and repeated exposures through 168 h post-exposure with the highest concentrations found at each interval in urine.

An AUC analysis for expired volatiles is presented in **Table XV.** Following a single exposure, approximately 53% of the total radioactivity in expired volatiles was attributed to metabolites. Graphical presentations of ^{14}C-HMDS and parent HMDS concentrations in expired volatiles and of radioactivity in urine, feces and as CO_2 are presented in **Figures 11-14**. Additional disposition kinetic parameters for total ^{14}C-HMDS and/or parent HMDS in expired volatiles, feces, urine and CO_2 (t_{max}, C_{max}, and $t_{1/2}$) are presented in **Table XVI.** The maximum concentration of radioactivity found in expired volatiles was in the first 0-1 hour collection interval following the single or repeated exposures. Following a single exposure the maximum concentration of radioactivity in feces was found in the 12-24 h post-exposure interval and in the 6-12 h post-exposure interval in urine. The highest concentration of $^{14}CO_2$ was found in the first interval, 0-24 h post-exposure. Half-lives of elimination for radioactivity were similar for expired volatiles, feces, urine and CO_2 between the single (range of 16-22 h) and repeated (range of 15-19 h) exposure groups.

Statistical analyses were conducted comparing the calculated AUCs for the single vs the repeated exposures for radioactivity in feces, urine, expired volatiles and CO_2

(**Appendix D**). Statistical significance was demonstrated between the single and the repeated exposures for radioactivity in feces, expired volatiles and CO_2 (**Appendix D**).

6. Urine Analysis

The percentages of the peaks that comprised total radioactivity in the urinary profiles can be found in **Table XIII**. This table shows the mean percent of radioactivity that can be attributed to individual metabolites from urine at 0-6, 6-12, and 12-24 hours following single exposure and 0-12 and 12-24 hours following repeat exposure. **Figure 15** shows representative chromatograms of a solvent standard, 0-12-hour urine samples from repeat exposure and 6-12-hour urine sample from single exposure. The radioactivity eliminated in the urine consisted entirely of polar metabolites of HMDS. No parent HMDS was found in any of the urine samples at any of the time points investigated. Individual animal results from the qualitative metabolite profile analysis can be found in **Appendix C**.

Only metabolites more polar than HMDS were detected in urine. Following the single exposure (6-12 h collection interval), the primary metabolites were 1,3-bis(hydroxymethyl)tetramethyldisiloxane and an unknown metabolite, with retention times of 25 min and 26.5 min, respectively. The primary metabolite following the single exposure, 0-6 and 12-24 h collection intervals was an unknown metabolite with a retention time of 26.5 min. Primary metabolites detected in urine in the 0-12 h and 12-24 h collection intervals following a repeated exposure to HMDS were 1,3-bis(hydroxymethyl)tetramethyldisiloxane and hydroxymethyldimethylsilanol. Other metabolites that were detected at greater than 4% of the total urinary radioactivity following both the single and repeated exposures were dimethylsilanediol and trimethylsilanol.

IV. SUMMARY / DISCUSSION / CONCLUSIONS

The purpose of this study was to evaluate the ADME and obtain kinetic parameters of hexamethyldisiloxane (HMDS) in male Fischer 344 rats following a single exposure to 5000 ppm ^{14}C-HMDS and fourteen days of exposure to a target concentration of 5000 ppm HMDS

followed by a single exposure to 5000 ppm ^{14}C-HMDS on exposure day fifteen. Concentrations were 99.8 and 100.5% of the targeted concentrations for single and repeat exposures, respectively.

Retention of HMDS at the end of exposure (body burden) was 3.6% and 3.8% for the single and repeated exposures, respectively. The greatest percentage of radioactivity was recovered in the urine; 46% and 64% following the single and repeated exposures, respectively. Forty-six percent and 28% was recovered in expired volatiles for the single and repeated exposures, respectively. In the feces ~2% was found in the recovered dose following the single and repeated exposure groups. In the carcass 3.8% and 2.7% of the dose was recovered following the single and repeat exposure. In both exposure groups, ~0.15% was recovered in brain, fat, liver, lung, kidney, and testes. $^{14}CO_2$ represented ~2% of the recovered body burden for both exposure scenarios.

Radioactivity was distributed to the tissues; brain, fat, kidney, liver, lung and testes with the highest concentrations found in fat, kidney and liver. Based on calculated AUCs, the ug eq HMDS/g*h, in fat, kidney, and liver following a single exposure were 58090, 5690 and 4225, respectively. Following repeated exposure the AUCs calculated for radioactivity in fat, kidney, and liver were 42671, 4979 and 3939, respectively. Parent HMDS was measured in blood and tissues; brain, fat, kidney, liver, lung and testes and the highest concentrations were found in fat and kidney. Based on calculated AUCs, the ug HMDS/g*h, in fat and kidney following a single exposure were 47939 and 2198, respectively. Following repeated exposure the AUCs for HMDS in fat and kidney were 94058 and 3081, respectively.

Elimination of radioactivity from blood and tissues (excluding fat) was multi-phasic, with the majority of the radioactivity eliminated within 24 h post-exposure. Elimination half-lives for radioactivity and parent HMDS were similar between the single exposure and the repeated exposure groups. The terminal half-life for elimination of radioactivity from blood was ~ 36 h and 39 h for the single and repeated exposures, respectively. Terminal half-lives of elimination for radioactivity of over 40 h were measured in liver, lung and testes after the single exposure and in liver, lung, testes and brain after repeated exposures.

In general, half-lives of elimination were 1 to 3 fold faster for parent HMDS than radioactivity; notable was the faster elimination half-life of HMDS from lung tissue. Elimination of parent HMDS from blood and tissues was multi-phasic, with the majority of parent HMDS eliminated within 24 h post-exposure. In blood, parent HMDS was not measurable after 24 h post-exposure. Following a single exposure, the terminal half-life in blood was 59 h and the shortest half-life was found in lung, 16 h. Following the repeated exposures, the terminal half-life in blood was 37 h and that in lung was 18 h. Parent HMDS time course data in blood, kidney, testes, liver, lung and fat following a single exposure to 5000 ppm HMDS are consistent with data reported by Durham and colleagues (2004) where tissues were analyzed for HMDS following a single non-radiolabeled exposure to 5000 ppm HMDS.

The primary route of elimination following a single exposure was in urine and expired volatiles, both at 46%; however, following repeated exposures the percentage excreted in the urine increased to 64% while the expired volatiles decreased to 28%. The majority of the radioactivity eliminated in urine, expired volatiles, CO_2 and feces was eliminated by 24 h post-exposure. Following a single exposure terminal half-lives of elimination were 19, 16, 18 and 22 h for expired volatiles, feces, urine and CO_2, respectively. Terminal half-lives of elimination were 19, 19, 15 and 17 h for expired volatiles, feces, urine and CO_2, respectively following repeated exposures.

Parent HMDS was measured in expired volatiles and based on AUC calculations, 47% of the total radioactivity in expired volatiles was attributed to parent HMDS in the single exposure. The percentage of parent HMDS in total ^{14}C-radioactivity in expired air remained constant throughout the collection intervals; at ~47 %. The percentage of parent HMDS in expired volatiles following repeated exposure could not be determined due to the elimination of residual parent HMDS from the 14 days of non-radiolabeled HMDS exposures.

Only metabolites of HMDS were detected in urine and these were determined to be polar metabolites. Primary metabolites detected in urine in the 0-12 h and 12-24 h collection intervals following a repeated exposure to HMDS were 1,3-

bis(hydroxymethyl)tetramethyldisiloxane and hydroxymethyldimethylsilanol. Following the single exposure (6-12 h collection interval), the primary metabolites were 1,3-bis(hydroxymethyl)tetramethyldisiloxane and an unknown metabolite, with retention times of 25 min and 26.5 min, respectively. The primary metabolite following the single exposure, 0-6 and 12-24 h collection intervals was an unknown metabolite with a retention time of 26.5 min. Other metabolites that were detected at greater than 4% of the total urinary radioactivity following both the single and repeated exposures were dimethylsilanediol and trimethylsilanol. These metabolites were also identified in urine following oral or i.v. administration (Varaprath et al., 2003). The aforementioned metabolites, except for trimethylsilanol are products of oxidative metabolism.

Statistical analyses were conducted comparing the calculated AUCs for the single vs the repeated exposures for both parent HMDS and radioactivity (**Appendix D**). Statistical significance was demonstrated between the single and the repeated exposures in the calculated AUCs for parent HMDS for the following tissues: fat, kidney, and testes. A statistical difference was also noted for radioactivity between the single and repeated exposure groups for blood, brain, fat, kidney, lung, testes, feces and urine.

HMDS has a low blood to air partition coefficient of ~ 1 and a high fat to blood partition coefficient of 321 (Dobrev et al., 2003). The low blood:air partitioning leads to rapid exhalation of HMDS and the high fat:blood partition coefficient leads to a slow redistribution of HMDS at the end of the exposure. In this study a rapid equilibration with blood occurred since the majority of the radioactivity immediately following exposure could be attributed to parent, with this decreasing over time to a small fraction attributable to parent from 24 to 168 h post-exposure.

Elimination of HMDS from the body occurs by exhalation and metabolism. The majority of the radioactivity was eliminated by 24 h post-exposure. Based on AUC calculations, approximately 47% of total expired radioactivity was parent HMDS for single exposure. Following single and repeated exposures the overall percentage of radioactivity in liver as

metabolites was similar (~98%) indicating repeated exposures to HMDS did not appear to saturate liver metabolism.

Only metabolites more polar than HMDS were detected in the urine. Based on the increased percentage of the recovered dose in the urine following single verses a repeat exposure (46% to 64%) with a corresponding decrease in percentage of recovered dose in expired volatiles (46% to 28%), repeated exposures to HMDS appear to increase HMDS metabolism.

Data from this study supports the observations in other studies with HMDS where an alpha 2u-globulin mechanism for renal toxicity in male rats has been noted (Cassidy et al., 2001; Jovanovic et al., 2005). The percentage of total radioactivity in kidney as parent HMDS, increased from ~39% to ~62% following the single and repeated exposure, respectively. The ratio of parent AUC in kidney to parent AUC in blood was ~30-fold higher than the same ratio calculated for liver tissue. This observation is consistent with the hypothesis that HMDS is an alpha 2u-globulin ligand and with a previous observation of increased alpha 2u-globulin in the kidney after exposure to HMDS.

The data from these experiments provide insight into the pharmacokinetics of HMDS. After single exposure and repeated exposure to 5000 ppm HMDS, approximately 4% of the dose was retained. Parent HMDS was measured in blood and tissues; brain, fat, kidney, liver, lung and testes and the highest concentrations were found in fat and kidney. Elimination of radioactivity from blood and tissues (excluding fat) was multi-phasic, with the majority of the radioactivity eliminated within 24 h post-exposure. The majority of systemically absorbed HMDS was eliminated in the urine or expired volatiles. Urinary elimination was entirely polar metabolites. Considering the effective removal of HMDS through metabolism and exhalation, accumulation in the body after repeated exposures is unlikely despite its high lipophilicity. The data from this study will be used to further refine PBPK models for HMDS.

V. ARCHIVE

Study related records, inclusive of, but not limited to, study authorization, study correspondence, study protocol (including amendments and deviations), the study schedule,

test article documentation, animal use authorization records, animal identification records, observation records, equipment verification records, reagent material safety data sheets, dosing records, sample collection records, sample preparation records, Excel worksheets, and the final report, will be maintained in the archives of Dow Corning Corporation, Midland, MI.

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TABLE I – Organization of Test Groups

Repeat Exposure							
Group Number	**Group Description**	**Number of Animals**	**Treatment**	**Target HMDS Exposure Conc. (ppm)**	**Blood Collections during ^{14}C-HMDS exposure (Hours)**	**Blood and Tissue Collections post ^{14}C-HMDS exposure (Hours)**	**Exposure Days**
1	Excreta Control	1 M	Control	0	NA	168*	NA
2	Body Burden Control	1 M	Control	0	NA	NA	NA
3	Body Burden	4 M	HMDS	5000	NA	NA	15
4	Tissue Distribution	40 M	HMDS	5000	3[a]	0*, 10 min[a], 30 min[a], 1[a], 2*, 12*, 24*, 72*, 120*	15
5	Excreta	5 M	HMDS	5000	NA	168*	15
6	Body Burden Spares	4 M	HMDS	5000	NA	NA	15
Single Exposure							
Group Number	**Group Description**	**Number of Animals**	**Treatment**	**Target HMDS Exposure Conc. (ppm)**	**Blood Collections during ^{14}C-HMDS exposure (Hours)**	**Blood and Tissue Collections post ^{14}C-HMDS exposure (Hours)**	**Exposure Days**
7	Excreta Control	1 M	Control	0	NA	168*	NA
8	Body Burden Control	1 M	Control	0	NA	NA	NA
9	Body Burden	4 M	HMDS	5000	NA	NA	1
10	Tissue Distribution	40 M	HMDS	5000	3[a]	0*, 10 min[a], 30 min[a], 1[a], 2*, 12*, 24*, 72*, 120*	1
11	Excreta	5 M	HMDS	5000	NA	168*	1
12	Body Burden Spares	4 M	HMDS	5000	NA	NA	1

Conc. = Concentration M = male

* = Terminal sacrifice time points, with blood and tissues collected

[a] = Terminal sacrifice time points, with blood collected

TABLE II – Summary of Chamber Homogeneity Evaluation

	Concentration HMDS in ppm						
Port Sampled	Sample 1	Sample 2	Sample 3	Port Mean	Port Std. Dev.	Nominal ppm HMDS	% difference from nominal
level 1-1	4997.7	4888.4	4959.4	4948.5	55.5	4944	0.09
level 2-1	4975.2	5116.7	4942.2	5011.4	92.7	4944	1.36
level 3-1	5040.0	5053.0	4962.2	5018.4	49.1	4944	1.50
level 4-1	5020.7	4889.0	4954.7	4954.8	65.8	4944	0.22
level 5-1	4976.3	4998.6	4973.7	4982.8	13.7	4944	0.79
level 6-1	4951.4	4964.9	4968.8	4961.7	9.1	4944	0.36
level 7-1	4933.8	5034.6	4943.3	4970.6	55.7	4944	0.54
Averages	4985.0	4992.2	4957.8	4978.3	48.8	4944	0.69
SEM	14.12	32.07	4.52	10.35	NA	NA	NA

Average Conditions During Evaluation	
Percent Oxygen	20.7%
Temperature	22.2 °C
Humidity	28.6%
Airflow	28.1 LPM

TABLE III – Summary of Environmental Conditions during the Exposure Periods

Repeat Expsoure

	Temperature (°C)				Humidity (%RH)				Air Flow (LPM)			
Exposure Day	Mean	SD	Max	Min	Mean	SD	Max	Min	Mean	SD	Max	Min
1	23.3	1.04	24.4	21.3	24.6	2.45	28.9	21.5	28.1	0.00	28.1	28.1
2	23.2	0.99	24.0	20.6	25.3	2.21	30.1	22.9	28.1	0.00	28.1	28.1
3	22.8	0.66	23.7	21.1	27.1	1.93	32.1	25.4	28.1	0.00	28.1	28.1
4	23.2	0.77	23.9	21.6	26.0	2.24	31.0	24.0	28.1	0.00	28.1	28.1
5	23.3	0.74	23.9	21.2	26.0	2.31	32.8	24.0	28.1	0.00	28.1	28.1
6	23.8	0.81	24.4	21.5	24.4	2.58	31.5	22.0	28.4	0.40	28.7	27.5
7	22.8	0.82	23.6	20.9	25.9	2.39	32.0	23.3	28.1	0.00	28.1	28.1
8	23.1	0.70	24.0	21.5	26.2	1.73	30.3	23.6	28.1	0.00	28.1	28.1
9	22.7	0.48	23.1	21.4	26.6	1.84	31.0	24.8	28.1	0.00	28.1	28.1
10	22.6	0.60	23.1	21.0	26.9	1.82	31.5	24.2	28.1	0.00	28.1	28.1
11	22.5	0.39	23.0	21.4	27.4	1.55	31.1	25.7	28.1	0.00	28.1	28.1
12	22.3	0.49	22.8	21.2	26.7	1.90	31.2	23.9	28.1	0.00	28.1	28.1
13	22.4	0.66	23.6	20.9	27.3	1.97	32.1	24.9	28.1	0.00	28.1	28.1
14	22.1	0.38	22.7	21.4	26.1	2.10	31.0	23.1	28.1	0.17	28.1	27.5
15	21.9	0.56	22.7	21.0	26.7	1.77	30.0	24.6	28.1	0.00	28.1	28.1
Mean	22.8	0.67	23.5	21.2	26.2	2.05	31.1	23.9	28.1	0.04	28.1	28.0

Single Expsoure

	Temperature (°C)				Humidity (%RH)				Air Flow (LPM)			
Exposure Day	Mean	SD	Max	Min	Mean	SD	Max	Min	Mean	SD	Max	Min
1	23.2	0.56	23.9	22.2	28.2	1.80	32.3	25.7	28.0	0.00	28.0	28.0

TABLE IV – Summary of Chamber Concentrations During Exposure Periods

Repeat Exposure

Measured Parameter	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	**Means (day 1-14)**	Day 15	**Means (days 1-15)**
Mean Measured Chamber Concentration (ppm)	5037	5114	5096	5046	5055	4833	4893	4926	4961	4896	5080	5048	4987	5011	4999	5365	5023
Standard Deviation (ppm)	90.9	63.4	79.8	98.0	74.6	113.3	77.0	86.5	65.3	159.7	67.7	225.6	110.3	60.3	98.0	66.6	95.9
Equivalent Concentration (mg/L)	33.2	33.7	33.6	33.2	33.3	31.8	32.2	32.4	32.7	32.2	33.5	33.2	32.8	33.0	32.9	35.3	33.1
Standard Deviation (mg/L)	0.60	0.42	0.53	0.65	0.49	0.75	0.51	0.57	0.43	1.05	0.45	1.49	0.73	0.40	0.65	0.44	0.63
Number of Samples (n)	20	19	18	19	19	14	15	17	15	16	16	16	17	14		20	
% of Target Concentration	100.7	102.3	101.9	100.9	101.1	96.7	97.9	98.5	99.2	97.9	101.6	101.0	99.7	100.2	100.0	107.3	100.5
Calculated Nominal Concentration (ppm)	4930	4929	4927	4936	4930	4834	4889	4898	4802	4860	5126	5105	5143	5136	4960	5107	4970
Equivalent Concentration (mg/L)	32.5	32.5	32.4	32.5	32.5	31.8	32.2	32.3	31.6	32.0	33.8	33.6	33.9	33.8	32.7	33.6	32.7
Measured/Nominal Concentration (%)	102.2	103.7	103.4	102.2	102.5	100.0	100.1	100.6	103.3	100.7	99.1	98.9	97.0	97.6	100.8	105.0	101.1

Single Exposure

Measured Parameter	Day 1
Mean Measured Chamber Concentration (ppm)	4989
Standard Deviation (ppm)	189.6
Equivalent Concentration (mg/L)	32.9
Standard Deviation (mg/L)	1.25
Number of Samples (n)	18
% of Target Concentration	99.8
Calculated Nominal Concentration (ppm)	5130
Equivalent Concentration (mg/L)	33.8
Measured/Nominal Concentration (%)	97.2

TABLE V – Calculated Achieved ^{14}C-HMDS Dose for Male Fischer 344 Rats Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

Sex / Exposure		Average Terminal Body Weights (g)	Average Respiratory Minute Volume (ml/min.)a	Exposure Duration/ animal (min.)	Volume of Respired Air (liters)	Calculated Achieved Dose (µCi/animal)	Average Measured Body Burden (DPM)	Average Measured Body Burden (µCi)	Body Burden Dose (µCi/kg)	Body Burden as % of Achieved Dose
Male Repeat	Average	212.9	117.0	360.0	42.1	82.0	6979556	3.1	14.8	3.8
	St. Dev.	9.65	3.97	NA	1.43	2.78	1502820.3	0.68	3.35	0.86
Male Single	Average	212.5	116.9	360.0	42.1	66.5	5369562	2.4	11.4	3.6
	St. Dev.	7.37	3.05	NA	1.10	1.73	460232.7	0.21	0.68	0.24

(a) Repiratory minute volume determined using the following equation: $2.1 \times BW(g)^{0.75}$

(b) Calculated Achieved Dose = Respiratory Minute Volume (ml/min.) x exposure duration (minutes) x 1L/1000ml x Exposure Concentration (mg/L) x Specific Activity (mCi/g)

Male Repeat	Achieved Mean ^{14}C-HMDS vapor Concentration =	35.41	mg/L		
	Specific Activity of Dosing Solution =	122.1	dpm/ug or	0.055	mCi/g
Male Single	Achieved Mean ^{14}C-HMDS vapor Concentration =	32.93	mg/L		
	Specific Activity of Dosing Solution =	106.6	dpm/ug	0.048	mCi/g

TABLE VI - Summary of Parent and Radioactivity HMDS Concentrations in Blood During and Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

BLOOD REPEAT EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
-3	11.78 ± 0.524	4	4	20.93 ± 2.371	4	4
0	12.44 ± 0.514	4	4	98.35 ± 3.703	4	4
0.17	5.89 ± 0.306	4	4	97.64 ± 8.909	4	4
0.5	2.87 ± 0.162	4	4	101.34 ± 4.557	4	4
1	2.06 ± 0.205	4	4	93.55 ± 7.552	4	4
2	1.28 ± 0.033	4	4	109.68 ± 8.332	4	4
12	0.46 ± 0.024	4	4	22.69 ± 1.039	4	4
24	0.40 ± 0.065	4	4	8.91 ± 0.487	4	4
72	BLQ NA	4	0	2.02 ± 0.059	4	4
120	BLQ NA	4	0	1.15 ± 0.091	4	4
168	BLQ NA	5	0	1.03 ± 0.042	5	5

BLOOD SINGLE EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
-3	11.07 ± 0.317	4	4	12.84 ± 1.568	4	4
0	11.58 ± 0.438	4	4	28.62 ± 1.293	4	4
0.17	6.34 ± 0.245	4	4	22.64 ± 0.689	4	4
0.5	2.75 ± 0.117	4	4	30.24 ± 2.868	4	4
1	2.28 ± 0.150	4	4	25.38 ± 2.633	4	4
2	1.44 ± 0.052	4	4	37.00 ± 4.872	4	4
12	0.45 ± 0.051	4	4	19.25 ± 1.573	4	4
24	0.39 ± 0.040	4	4	9.07 ± 0.287	4	4
72	BLQ NA	4	0	1.97 ± 0.088	4	4
120	BLQ NA	4	0	0.92 ± 0.085	4	4
168	BLQ NA	5	0	0.99 ± 0.139	5	5

NOTE: negative time point took place during exposure
BLQ = Below Limit of Quantitation

TABLE VII - Summary of Parent and Radioactivity HMDS Concentrations in Brain Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

BRAIN REPEAT EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	150.85 ± 4.410	4	4	206.91 ± 2.608	4	4
2	11.49 ± 0.483	4	4	107.24 ± 8.109	4	4
12	1.58 ± 0.079	4	4	21.04 ± 1.100	4	4
24	1.01 ± 0.049	4	4	7.76 ± 0.610	4	4
72	0.20 ± 0.023	4	4	2.16 ± 0.239	4	4
120	0.06 ± 0.003	4	4	1.02 ± 0.152	4	4
168	0.04 ± 0.009	5	5	1.06 ± 0.144	5	5

BRAIN SINGLE EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	129.57 ± 3.252	4	4	161.62 ± 1.958	4	4
2	10.98 ± 1.048	4	4	59.69 ± 3.458	4	4
12	1.57 ± 0.118	4	4	26.59 ± 1.165	4	4
24	0.84 ± 0.051	4	4	10.38 ± 0.286	4	4
72	0.16 ± 0.014	4	4	1.61 ± 0.093	4	4
120	0.05 ± 0.001	4	4	0.60 ± 0.189	4	4
168	0.03 NA	5	1	0.73 ± 0.101	5	5

BLQ = Below Limit of Quantitation

TABLE VIII – Summary of Parent and Radioactivity HMDS Concentrations in Kidney Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

KIDNEY REPEAT EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	280.89 ± 15.068	4	4	338.74 ± 12.958	4	4
2	75.05 ± 7.611	4	4	238.51 ± 9.518	4	4
12	52.78 ± 2.993	4	4	95.57 ± 2.596	4	4
24	47.51 ± 2.773	4	4	55.48 ± 1.638	4	4
72	10.62 ± 1.014	4	4	11.18 ± 0.965	4	4
120	2.34 ± 0.527	4	4	5.73 ± 0.626	4	4
168	0.70 ± 0.110	5	5	4.67 ± 0.437	5	5

KIDNEY SINGLE EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	172.74 ± 4.548	4	4	234.40 ± 5.936	4	4
2	54.22 ± 1.685	4	4	161.17 ± 5.187	4	4
12	31.04 ± 3.653	4	4	91.67 ± 2.814	4	4
24	37.28 ± 3.197	4	4	73.73 ± 4.809	4	4
72	7.21 ± 0.674	4	4	20.30 ± 0.928	4	4
120	1.49 ± 0.132	4	4	8.87 ± 0.474	4	4
168	0.37 ± 0.218	5	5	6.83 ± 0.538	5	5

BLQ = Below Limit of Quantitation

TABLE IX – Summary of Parent and Radioactivity HMDS Concentrations in Testes Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS.

TESTE REPEAT EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	62.83 ± 1.572	4	4	132.10 ± 1.865	4	4
2	30.20 ± 11.873	4	4	119.57 ± 8.154	4	4
12	5.81 ± 1.627	4	4	27.13 ± 1.023	4	4
24	7.30 ± 3.205	4	4	10.81 ± 1.105	4	4
72	1.43 ± 0.292	4	4	3.80 ± 0.418	4	4
120	4.23 ± 2.392	4	4	3.37 ± 0.423	4	4
168	0.88 ± 0.286	5	5	2.07 ± 0.183	5	5

TESTE SINGLE EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	39.62 ± 1.033	4	4	30.20 ± 1.283	4	4
2	6.11 ± 0.553	4	4	25.82 ± 0.581	4	4
12	3.06 ± 1.195	4	4	14.51 ± 0.542	4	4
24	1.92 ± 0.679	4	4	6.52 ± 0.329	4	4
72	1.27 ± 0.873	4	4	1.78 ± 0.284	4	4
120	1.35 ± 1.111	4	2	1.38 ± 0.259	4	4
168	0.29 ± 0.192	5	2	1.17 ± 0.061	5	5

BLQ = Below Limit of Quantitation

TABLE X – Summary of Parent and Radioactivity HMDS Concentrations in Liver Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

LIVER REPEAT EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	327.02 ± 31.976	3	3	260.57 ± 5.545	3	3
2	5.40 ± 0.651	4	4	206.30 ± 15.648	4	4
12	2.10 ± 0.750	4	4	61.35 ± 5.625	4	4
24	0.38 ± 0.085	4	4	32.58 ± 1.623	4	4
72	0.09 ± 0.011	4	4	13.64 ± 0.478	4	4
120	0.05 ± 0.005	4	4	6.95 ± 0.545	4	4
168	0.02 ± 0.003	5	5	5.91 ± 0.263	5	5

LIVER SINGLE EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	86.35 ± 6.704	4	4	182.74 ± 0.723	4	4
2	5.45 ± 2.600	4	4	128.29 ± 6.071	4	4
12	1.10 ± 0.311	4	4	88.24 ± 2.601	4	4
24	0.56 ± 0.070	4	4	47.23 ± 0.884	4	4
72	0.09 ± 0.016	4	2	12.55 ± 0.800	4	4
120	0.02 NA	4	1	7.49 ± 0.552	4	4
168	0.01 NA	5	1	6.43 ± 0.441	5	5

BLQ = Below Limit of Quantitation

TABLE XI – Summary of Parent and Radioactivity HMDS Concentrations in Lung Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

LUNG REPEAT EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	126.69 ± 7.462	4	4	155.12 ± 4.528	4	4
2	20.96 ± 2.052	4	4	105.97 ± 5.815	4	4
12	10.75 ± 0.967	4	4	27.30 ± 1.252	4	4
24	3.48 ± 0.201	4	4	10.62 ± 0.412	4	4
72	0.31 ± 0.022	4	4	4.44 ± 0.257	4	4
120	0.10 ± 0.012	4	4	3.19 ± 0.090	4	4
168	0.07 ± 0.005	5	5	2.64 ± 0.324	5	5

LUNG SINGLE EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	88.91 ± 3.052	4	4	141.48 ± 3.001	4	4
2	33.22 ± 8.165	4	4	92.94 ± 7.865	4	4
12	9.62 ± 1.457	4	4	47.31 ± 1.641	4	4
24	2.84 ± 0.350	4	4	24.21 ± 1.979	4	4
72	0.26 ± 0.039	4	4	9.14 ± 0.789	4	4
120	BLQ NA	4	0	7.31 ± 1.440	4	4
168	BLQ NA	5	0	5.42 ± 0.223	5	5

BLQ = Below Limit of Quantitation

TABLE XII – Summary of Parent and Radioactivity HMDS Concentrations in Fat Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

FAT REPEAT EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	2646.92 ± 286.439	4	4	1193.89 ± 138.033	4	4
2	3235.90 ± 333.086	3	3	1259.86 ± 113.862	3	3
12	1916.59 ± 337.101	4	4	859.49 ± 93.972	4	4
24	1493.66 ± 144.539	4	4	508.02 ± 63.665	4	4
72	159.94 ± 16.549	4	4	142.99 ± 14.226	4	4
120	46.30 ± 11.590	4	4	63.52 ± 9.777	4	4
168	10.34 ± 2.572	5	5	43.12 ± 6.102	5	5

FAT SINGLE EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
0	1527.93 ± 115.533	4	4	1530.82 ± 127.624	4	4
2	1371.54 ± 55.025	4	4	1383.57 ± 42.837	4	4
12	911.38 ± 85.279	4	4	920.38 ± 82.456	4	4
24	698.64 ± 36.819	4	4	720.42 ± 35.742	4	4
72	154.79 ± 21.605	4	4	231.57 ± 20.544	4	4
120	34.85 ± 5.176	4	4	114.39 ± 4.406	4	4
168	7.55 ± 2.954	5	5	83.75 ± 4.020	5	5

BLQ = Below Limit of Quantitation

TABLE XIII – Summary of Parent and Radioactivity HMDS Concentrations in Expired Volatiles Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

EXPIRED VOLATILES REPEAT EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/hr ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /hr ± std error)	n	n above BLQ
1	6660.97 ± 359.427	5	5	6059.26 ± 401.968	5	5
2	2448.21 ± 57.533	5	5	2116.36 ± 68.445	5	5
4	1336.17 ± 67.921	5	5	1301.20 ± 69.419	5	5
6	855.98 ± 47.190	5	5	851.76 ± 33.155	5	5
12	431.87 ± 19.059	5	5	408.92 ± 15.303	5	5
24	255.10 ± 36.524	5	5	167.36 ± 10.383	5	5
48	117.36 ± 6.867	5	5	81.80 ± 7.241	5	5
72	50.43 ± 3.181	5	5	31.47 ± 2.489	5	5
96	23.14 ± 2.217	5	5	13.43 ± 1.334	5	5
120	15.56 ± 4.744	5	5	6.53 ± 0.803	5	5
144	5.75 ± 0.784	5	5	3.25 ± 0.478	5	5
168	3.91 ± 0.538	5	5	1.72 ± 0.270	5	5

EXPIRED VOLATILES SINGLE EXPOSURE						
	Males Parent			Males Radioactivity		
time point (hr)	HMDS Concentration (µg/hr ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /hr ± std error)	n	n above BLQ
1	3382.79 ± 94.247	5	5	6971.51 ± 210.373	5	5
2	1274.25 ± 64.827	5	5	2641.77 ± 137.568	5	5
4	788.00 ± 23.622	5	5	1668.10 ± 58.009	5	5
6	471.83 ± 36.110	5	5	1013.66 ± 77.290	5	5
12	247.14 ± 10.663	5	5	525.18 ± 20.407	5	5
24	135.67 ± 0.852	5	5	293.19 ± 5.170	5	5
48	55.41 ± 4.061	5	5	118.07 ± 10.007	5	5
72	17.47 ± 2.099	5	5	37.03 ± 4.355	5	5
96	8.51 ± 1.260	5	5	18.55 ± 2.629	5	5
120	4.11 ± 0.667	5	5	9.13 ± 1.499	5	5
144	2.10 ± 0.388	5	5	4.76 ± 0.933	5	5
168	1.15 ± 0.252	5	5	2.50 ± 0.551	5	5

BLQ = Below Limit of Quantitation

TABLE XIV – Summary of Radioactivity HMDS Concentrations in Urine, Feces, and KOH Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

Urine Males Radioactivity						
	Single Exposure			Repeat Exposure		
time point (hr)	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
6	2187.41 ± 161.282	5	5	NS N/AP	0	0
12	3347.98 ± 129.559	5	5	5026.10 ± 362.931	5	5
24	2200.11 ± 74.835	5	5	1638.51 ± 184.495	5	5
48	627.37 ± 57.439	5	5	387.04 ± 20.695	5	5
72	153.58 ± 11.951	5	5	109.30 ± 13.427	5	5
96	68.19 ± 8.028	5	5	51.44 ± 5.002	5	5
120	35.92 ± 4.819	5	5	28.03 ± 2.701	5	5
144	22.76 ± 3.195	5	5	18.31 ± 1.506	5	5
168	14.87 ± 1.738	5	5	12.02 ± 1.305	5	5

Feces Males Radioactivity						
	Single Exposure			Repeat Exposure		
time point (hr)	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /g ± std error)	n	n above BLQ
6	27.43 ± 10.837	2	2	NS N/AP	0	0
12	203.58 N/AP	1	1	85.88 ± 32.033	4	4
24	259.44 ± 30.903	5	5	216.49 ± 12.318	5	5
48	57.08 ± 6.346	5	5	49.66 ± 5.604	5	5
72	12.11 ± 4.258	5	5	15.81 ± 3.249	5	5
96	10.09 ± 6.598	5	5	9.02 ± 4.070	5	5
120	2.23 ± 1.295	5	5	5.11 ± 1.337	5	5
144	2.03 ± 1.250	5	5	3.26 ± 0.372	5	5
168	0.96 ± 0.964	5	5	2.99 ± 0.835	5	5

KOH Males Radioactivity						
	Single Exposure			Repeat Exposure		
time point (hr)	HMDS Concentration (µg Eq. /hr ± std error)	n	n above BLQ	HMDS Concentration (µg Eq. /hr ± std error)	n	n above BLQ
24	30.50 ± 2.816	5	5	53.42 ± 1.902	5	5
48	8.00 ± 0.398	5	5	5.27 ± 0.548	5	5
72	2.90 ± 0.258	5	5	3.31 ± 0.802	5	5
96	1.62 ± 0.140	5	5	1.29 ± 0.219	5	5
120	0.93 ± 0.094	5	5	0.69 ± 0.087	5	5
144	1.03 ± 0.162	5	5	0.26 ± 0.081	5	5
168	0.57 ± 0.087	5	5	0.56 ± 0.139	5	5

NS = No Sample
BLQ = Below Limit of Quantitation

TABLE XV - Summary of Area under the Curve (AUC) Data for Radioactivity and Parent HMDS in Blood, Tissues, and Expired Volatiles

	Repeated Exposure						
	Area Under the Curve (µg/g or µg Eq. /g * Hour)[a]				AUC HMDS tissue / AUC HMDS blood	Percent of ^{14}C	
	^{14}C-HMDS		HMDS			HMDS	Metabolites
Blood	1441.49	± 50.12	41.91	± 2.01	1	2.91	97.09
Brain	1249.72	± 51.63	137.03	± 3.37	3.3	10.96	89.04
Fat	42671.25	± 2411.8	94058.48	± 6070.71	2244.3	ND [b,c]	ND
Kidney	4979.26	± 95.54	3081.05	± 113.04	73.5	61.88	38.12
Liver	3938.64	± 121.91	98.85	± 9.74	2.4	2.51	97.49
Lung	1642.58	± 39.97	369.91	± 16.71	8.8	22.52	77.48
Testes	1685.07	± 63.79	747.22	± 165.08	17.8	44.34	55.66
Expired Volatiles	22160.23	± 420.44	26645.03	± 777.15	NA	ND	ND
	Single Exposure						
Blood	888.99	± 33.80	47.17	± 1.4	1.0	5.31	94.69
Brain	1069.05	± 26.64	124.51	± 6.15	2.6	11.65	88.35
Fat	58090.02	± 1747.71	47938.90	± 1825.82	1016.3	82.53	17.47
Kidney	5690.18	± 158.90	2198.38	± 109.66	46.6	38.63	61.37
Liver	4225.04	± 70.18	69.58	± 14.91	1.5	1.65	98.35
Lung	2689.18	± 109.38	403.72	± 48.85	8.6	15.01	84.99
Testes	679.37	± 22.04	226.62	± 56.12	4.8	33.36	66.64
Expired Volatiles	29316.10	± 527.79	13821.85	± 239.38	NA	47.15	52.85

a Mean ± SEM. Statistical significance between parent and radioactivity, $p<0.01$ for all tissues and expired volatiles, in each group.
In addition, statistical significance for HMDS AUCs between single and repeated exposures in fat, kidney, testes and expired volatiles.
Statistical significance for ^{14}C-HMDS AUCs between single and repeated exposure in blood, brain, fat, kidney, lung, testes and expired volatiles.
b ND = Not Done
c Values for fat in the repeated exposure rats were not determined as the accumulation of HMDS over the 14 days of non-radiolabeled HMDS exposure results in an accumulation of HMDS in the fat, which does not allow for a valid comparison to ^{14}C-HMDS

TABLE XVI - Summary of Disposition Kinetics for Radioactivity and Parent HMDS in Blood and Tissues from Repeat and Single Exposures

Radioactivity						
	Repeated Exposure			Single Exposure		
	C_{max} (µg Eq. HMDS/g)	T_{max} (h Post exposure)	$T_{1/2\ (terminal)}$ [a] (h)	C_{max} (µg Eq. HMDS/g)	T_{max} (h Post exposure)	$T_{1/2\ (terminal)}$ [a] (h)
Blood	109.68	2	38.61 ± 0.475	37.00	2	36.47 ± 0.537
Brain	206.91	0	41.15 ± 0.440	161.62	0	29.96 ± 0.688
Fat	1259.86	2	29.89 ± 0.394	1530.82	0	35.04 ± 0.315
Kidney	338.74	0	30.26 ± 0.522	234.40	0	36.70 ± 0.296
Liver	260.57	0	51.27 ± 0.236	182.74	0	42.38 ± 0.406
Lung	155.12	0	61.77 ± 0.234	141.48	0	59.25 ± 0.265
Testes	132.10	0	55.85 ± 0.271	30.20	0	48.67 ± 0.417
Charcoal	6059.26 µg Eq. /h	1	18.55 ± 0.292	6971.51 ug Eq. /h	1	18.97 ± 0.264
Feces	216.49	12-24	19.43 ± 0.634	259.44	12-24	16.06 ± 0.592
Urine	5026.10	0-12	15.32 ± 0.786	3347.98	6-12	17.66 ± 0.475
CO_2	53.42 ug Eq. /h	0-24	16.73 ± 0.926	30.50 ug Eq. /h	0-24	21.71 ± 0.600

Parent						
	Repeated Exposure			Single Exposure		
	C_{max} (µg HMDS/g)	T_{max} (h Post exposure)	$T_{1/2\ (terminal)}$ [a] (h)	C_{max} (µg HMDS/g)	T_{max} (h Post exposure)	$T_{1/2\ (terminal)}$ [a] (h)
Blood	12.44	0	36.87 ± 0.059	11.58	0	58.91 ± 0.015
Brain	150.85	0	26.35 ± 0.375	129.57	0	24.32 ± 0.437
Fat	3235.90	2	19.28 ± 0.252	1527.93	0	21.90 ± 0.060
Kidney	280.89	0	24.37 ± 0.099	172.74	0	23.10 ± 0.178
Liver	327.02	0	20.88 ± 0.929	86.35	0	19.56 ± 0.709
Lung	126.69	0	18.17 ± 0.877	88.91	0	15.97 ± 0.787
Testes	62.83	0	51.33 ± 0.721	39.62	0	39.78 ± 0.301
Charcoal	6660.97 µg/h	1	21.71 ± 0.193	3382.79 ug/h	1	18.82 ± 0.264
Feces	NA	NA	NA NA	NA	NA	NA NA
Urine	NA	NA	NA NA	NA	NA	NA NA
CO_2	NA	NA	NA NA	NA	NA	NA NA

[a] Mean ± SEM

TABLE XVII - Summary of Radioactivity Mass Balance as Percent of Body Burden and Percent of Recovered Dose following Repeat Nose-Only Vapor Inhalation Exposures to HMDS followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

Repeat Exposure Male N = 5	Blood	Carcass	Cone Rinse	Expired Volatiles	Feces	Hexane Rinse	KOH	THF Rinse	Urine	Tissues*	Total DPM's	Percent Recovery
Mean	52	244079	164343	2473742	145315	227	189893	1713	5729657	11740	8960761	128.4
SD	5.5	101860.1	171520.6	158481.1	43477.4	108.9	14379.4	1080.5	364826.2	1900.9	382263.8	5.5
SEM	2.5	45553.2	76706.3	70874.9	19443.7	48.7	6430.7	483.2	163155.2	850.1	170953.6	2.4
% Recovery	0.00	2.72	1.83	27.61	1.62	0.00	2.12	0.02	63.94	0.13	100.0	
% Body Burden	0.00	3.50	2.35	35.44	2.08	0.00	2.72	0.02	82.09	0.17	128.4	
%SEM Recovery	0.00	0.51	0.86	0.79	0.22	0.00	0.07	0.01	1.82	0.01	1.9	
%SEM Body Burden	0.00	0.65	1.10	1.02	0.28	0.00	0.09	0.01	2.34	0.01	2.4	

* equals total from tissues listed below

Repeat Exposure Male N = 5	Brain Extract	Brain Solub.	Kidney Extract	Kidney Solub.	Liver Extract	Liver Solub.	Lung Extract	Lung Solub.	Peri-renal Fat Extract	Peri-renal Fat Solub.	Testes Extract	Testes Solub.
Mean	79	139	255	696	681	5705	229	66	2832	419	157	482
SD	27.0	44.5	84.7	247.0	609.6	547.9	44.9	52.4	1085.6	185.7	80.7	48.2
SEM	12.1	19.9	37.9	110.5	272.6	245.0	20.1	23.4	485.5	83.0	36.1	21.6
% Recovery	0.00	0.00	0.00	0.01	0.01	0.06	0.00	0.00	0.03	0.00	0.00	0.01
% Body Burden	0.00	0.00	0.00	0.01	0.01	0.08	0.00	0.00	0.04	0.01	0.00	0.01
%SEM Recovery	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00
%SEM Body Burden	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00

Single Exposure Male N = 5	Blood	Carcass	Cone Rinse	Expired Volatiles	Feces	Hexane Rinse	KOH	THF Rinse	Urine	Tissues**	Total DPM's	Percent Recovery
Mean	38	231597	77235	2792633	93834	126	116422	1991	2793803	12430	6120110	114.0
SD	7.8	16230.4	45418.4	170173.7	9832.6	116.7	18250.2	382.6	174602.9	1870.9	302092.2	5.6
SEM	3.5	7258.5	20311.7	76104.0	4397.3	52.2	8161.7	171.1	78084.8	836.7	135099.7	2.5
% Recovery	0.00	3.78	1.26	45.63	1.53	0.00	1.90	0.03	45.65	0.20	100.0	
% Body Burden	0.00	4.31	1.44	52.01	1.75	0.00	2.17	0.04	52.03	0.23	114.0	
%SEM Recovery	0.00	0.12	0.33	1.24	0.07	0.00	0.13	0.00	1.28	0.01	2.2	
%SEM Body Burden	0.00	0.14	0.38	1.42	0.08	0.00	0.15	0.00	1.45	0.02	2.5	

** equals total from tissues listed below

Single Exposure Male N = 5	Brain Extract	Brain Solub.	Kidney Extract	Kidney Solub.	Liver Extract	Liver Solub.	Lung Extract	Lung Solub.	Peri-renal Fat Extract	Peri-renal Fat Solub.	Testes Extract	Testes Solub.
Mean	132	3	614	612	598	4871	67	461	4249	468	54	301
SD	34.6	6.0	141.7	118.8	439.4	680.7	60.3	34.2	1000.0	228.1	8.3	41.6
SEM	15.5	2.7	63.4	53.1	196.5	304.4	27.0	15.3	447.2	102.0	3.7	18.6
% Recovery	0.00	0.00	0.01	0.01	0.01	0.08	0.00	0.01	0.07	0.01	0.00	0.00
% Body Burden	0.00	0.00	0.01	0.01	0.01	0.09	0.00	0.01	0.08	0.01	0.00	0.01
%SEM Recovery	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00
%SEM Body Burden	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.01	0.00	0.00	0.00

TABLE XVIII - Summary of Urinary Metabolites as Percentages of the Total Urinary Radioactivity Following Fourteen Repeat Nose-Only Vapor Inhalation Exposures to HMDS Followed by a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS, additionally a Single Nose-Only Vapor Inhalation Exposure to ^{14}C-HMDS

Time Interval (h)		Hydroxymethyl-dimethylsilanol ~5.3 min. Retention time metabolite	Dimethyl-silanediol ~13.5min. Retention time metabolite	(1,3-Bis (hydroxymethyl) tetramethyldisiloxane) ~25.0min. Retention time metabolite	Unknown ~26.5min. Retention time metabolite	Unknown ~29.0min. Retention time metabolite	Unknown ~31.3min. Retention time metabolite	Trimethyl silanol ~32.2min. Retention time metabolite	Unknown ~32.9min. Retention time metabolite	Unknown ~33.9min. Retention time metabolite	Unknown ~37.0min. Retention time metabolite	Pentamethyl-disiloxanol ~38.4min. Retention time metabolite	Hydroxy methyl-pentamethyl-disiloxane ~39.2min. Retention time metabolite	Unknown back-ground counts
Single Exposure														
0-6	Mean	9%	13%	0%	61%	1%	1%	13%	0%	1%	NA	1%	NA	0%
	SD	2%	1%	0%	2%	2%	2%	2%	1%	1%	NA	1%	NA	1%
6-12	Mean	15%	14%	24%	33%	0%	1%	9%	2%	2%	NA	0%	NA	0%
	SD	1%	1%	3%	4%	1%	1%	2%	0%	0%	NA	0%	NA	1%
12-24	Mean	25%	21%	0%	47%	1%	0%	4%	1%	0%	NA	0%	NA	0%
	SD	1%	1%	0%	1%	1%	0%	1%	1%	0%	NA	0%	NA	0%
eated Exposure														
0-12	Mean	18%	12%	35%	8%	10%	NA	10%	3%	2%	0%	0%	1%	NA
	SD	2%	1%	3%	1%	2%	NA	1%	0%	0%	0%	0%	1%	NA
12-24	Mean	33%	26%	28%	7%	1%	NA	4%	1%	0%	0%	0%	0%	NA
	SD	3%	4%	6%	7%	2%	NA	2%	1%	0%	1%	0%	0%	NA

FIGURE 1 – Representative Chromatogram of Radiochemical Purity Evaluation

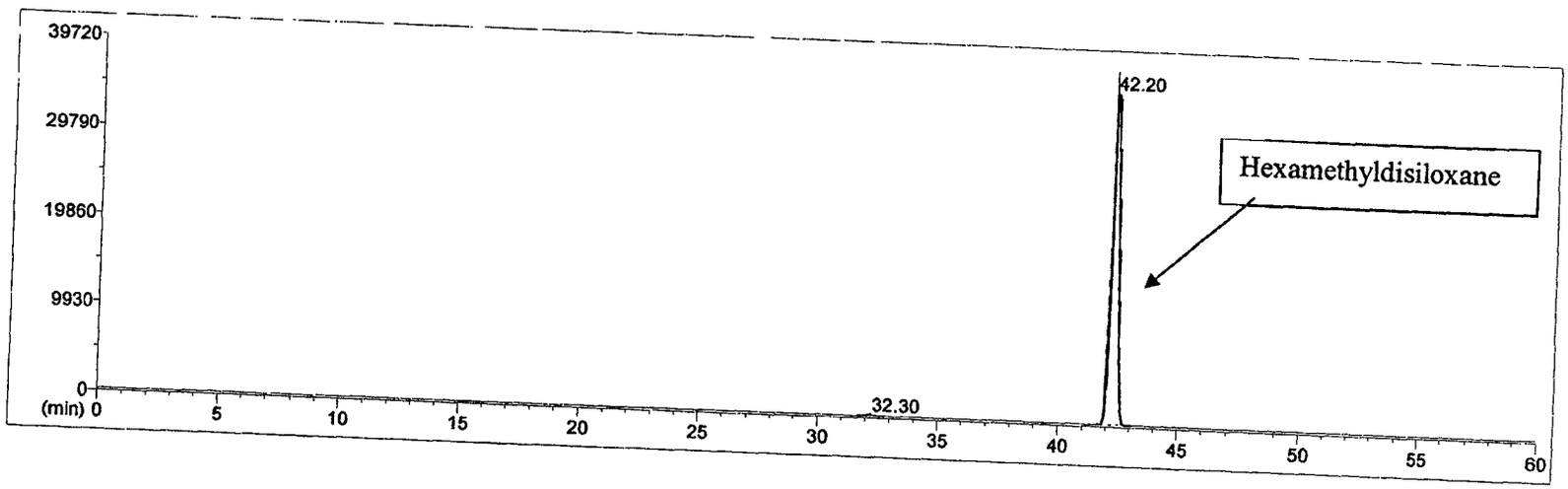


FIGURE 2 – Representative Chromatogram of On-line Inhalation Chamber Analysis

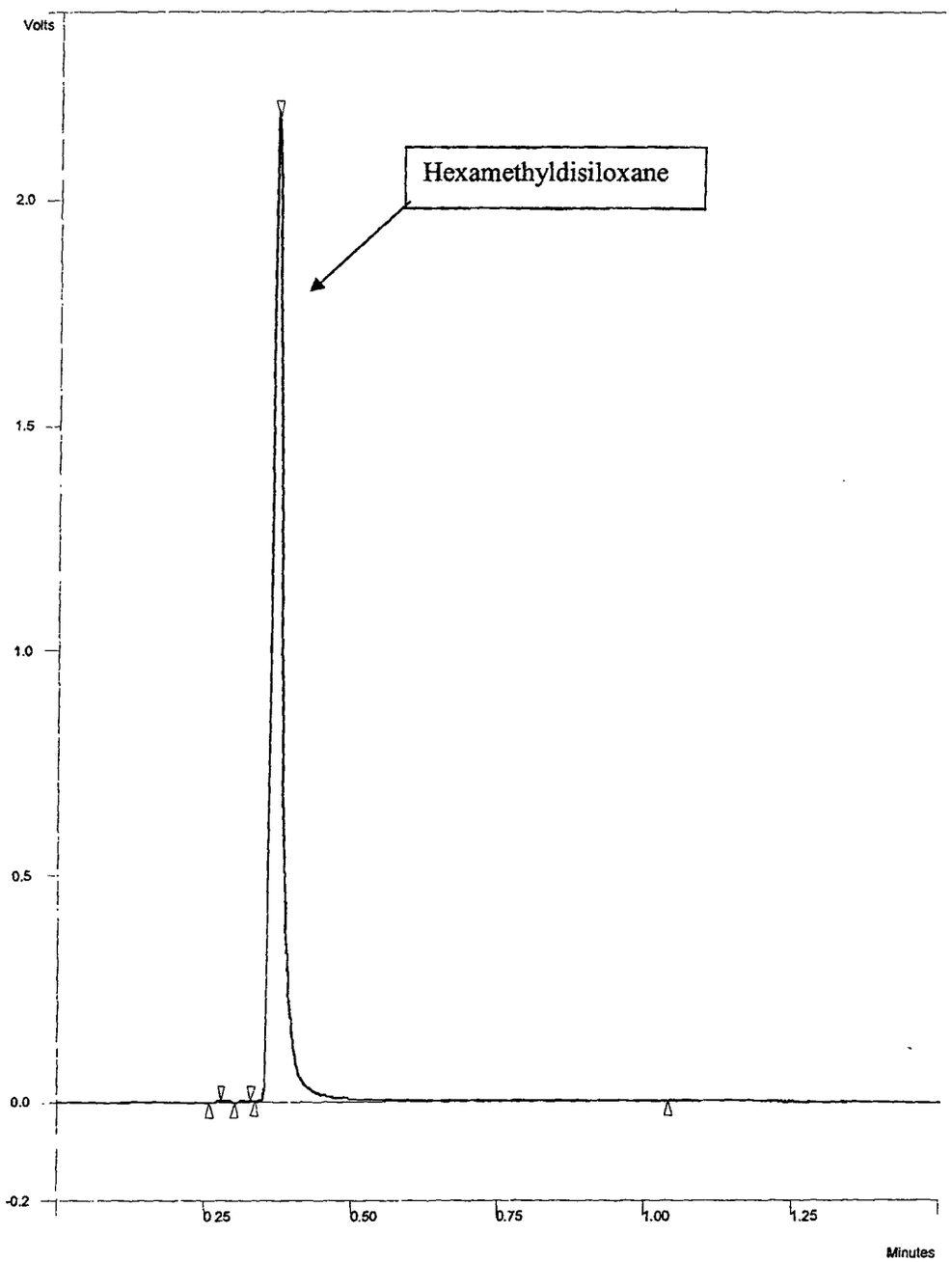


FIGURE 3 – Measured Chamber Concentrations during Nose-Only Vapor Inhalation Exposures

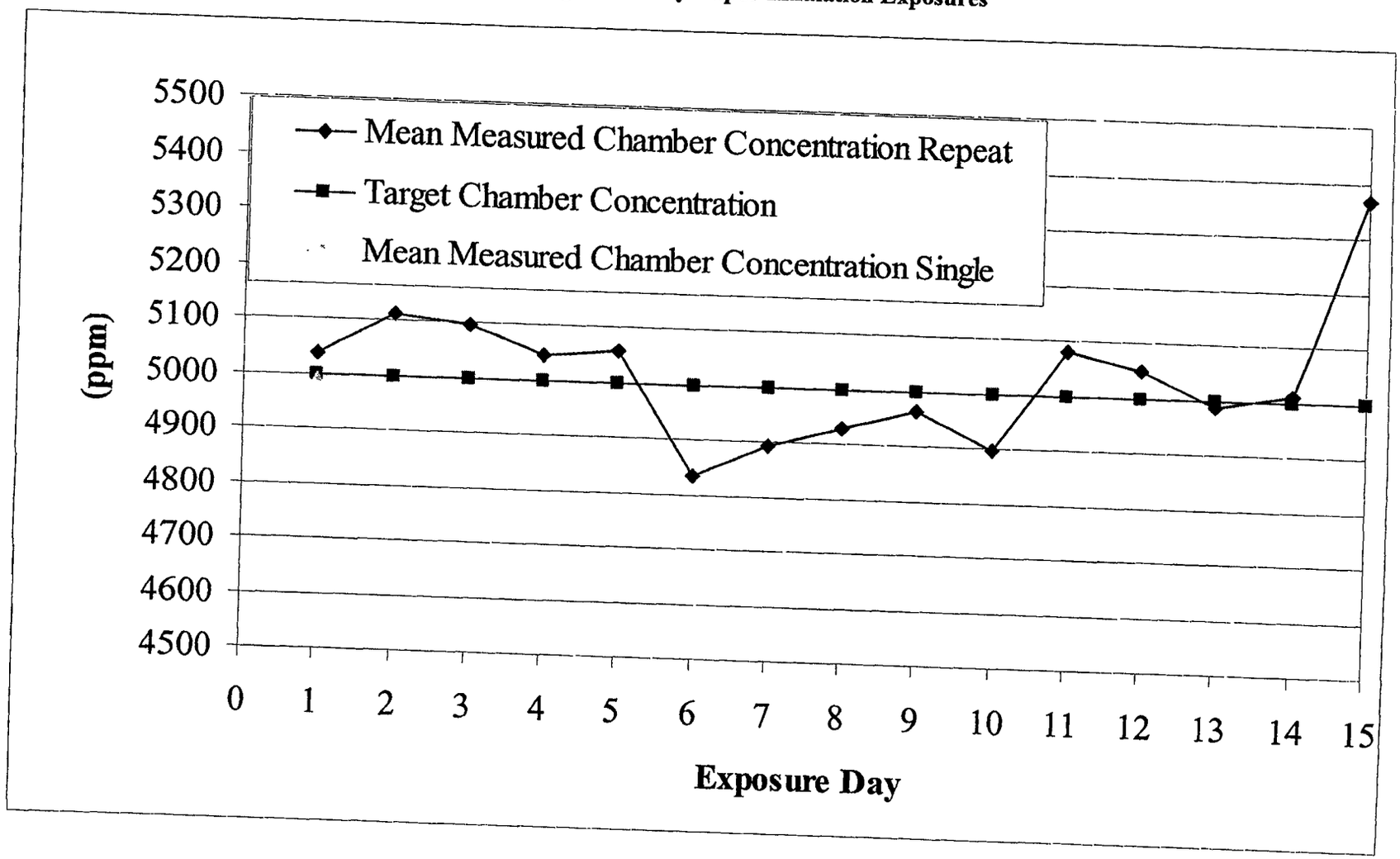


FIGURE 4 – Concentration of Parent HMDS and Radioactivity in Blood of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

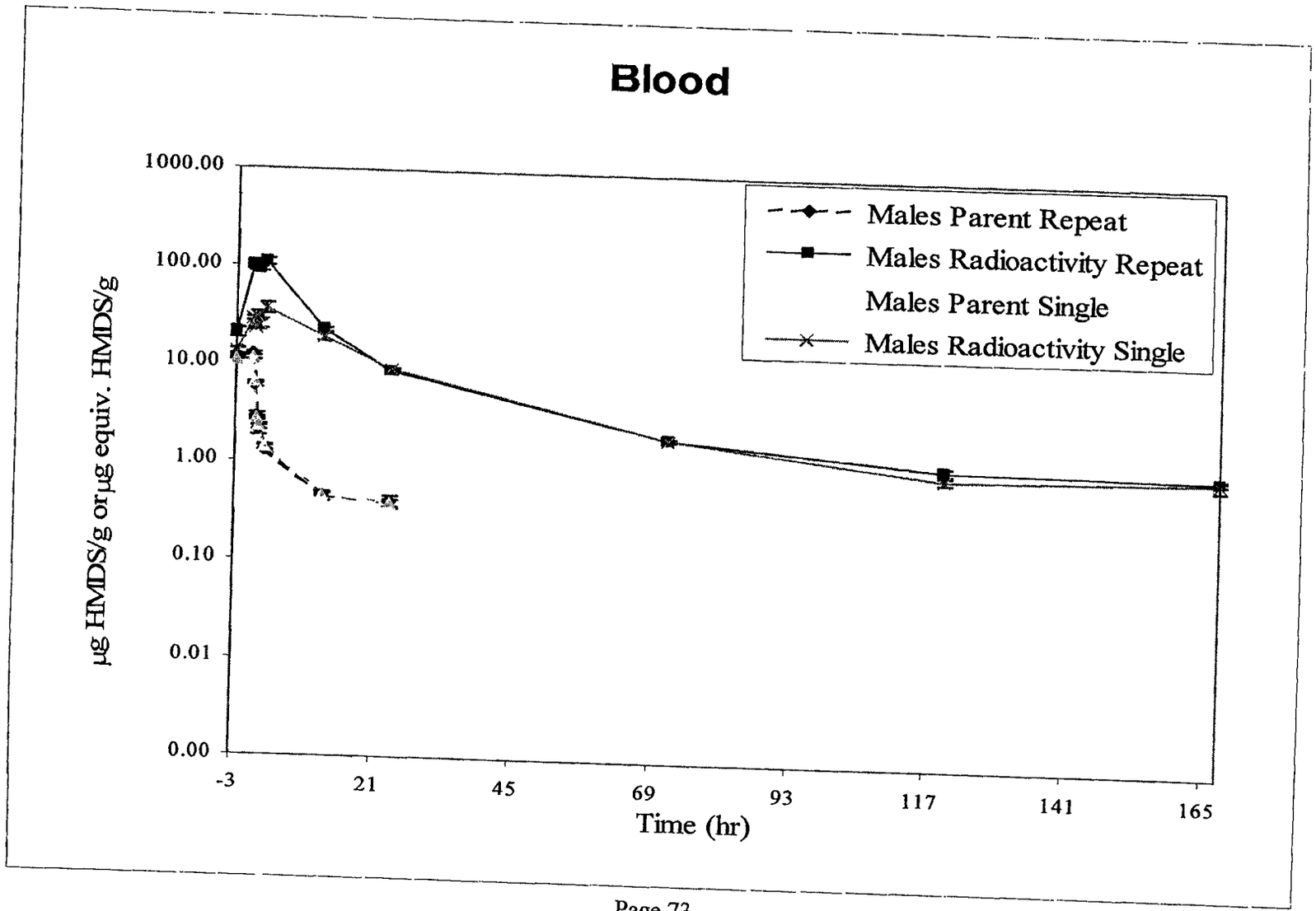


FIGURE 5 – Concentration of Parent HMDS and Radioactivity in Brain of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

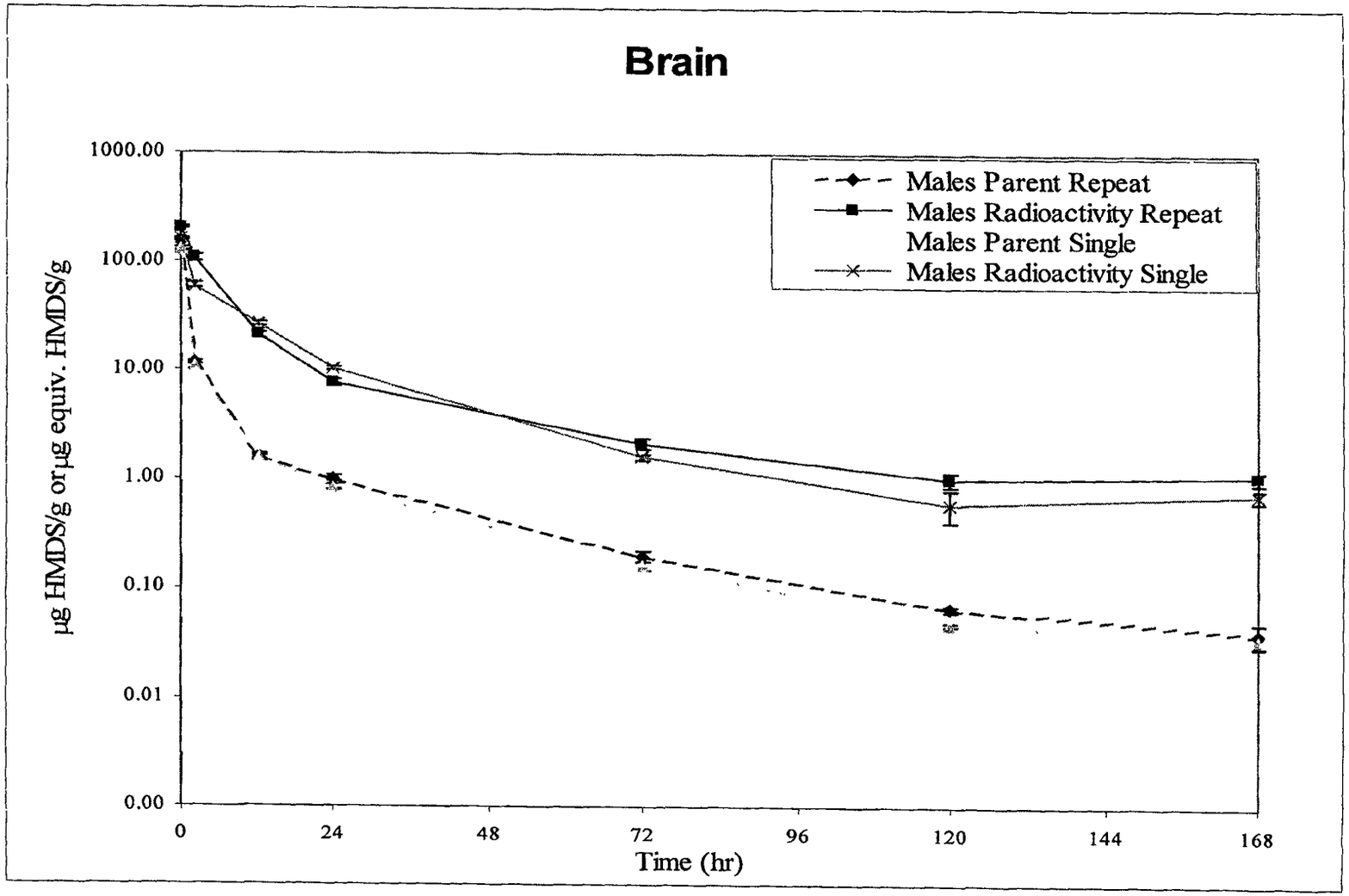


FIGURE 6 – Concentration of Parent HMDS and Radioactivity in Kidney of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

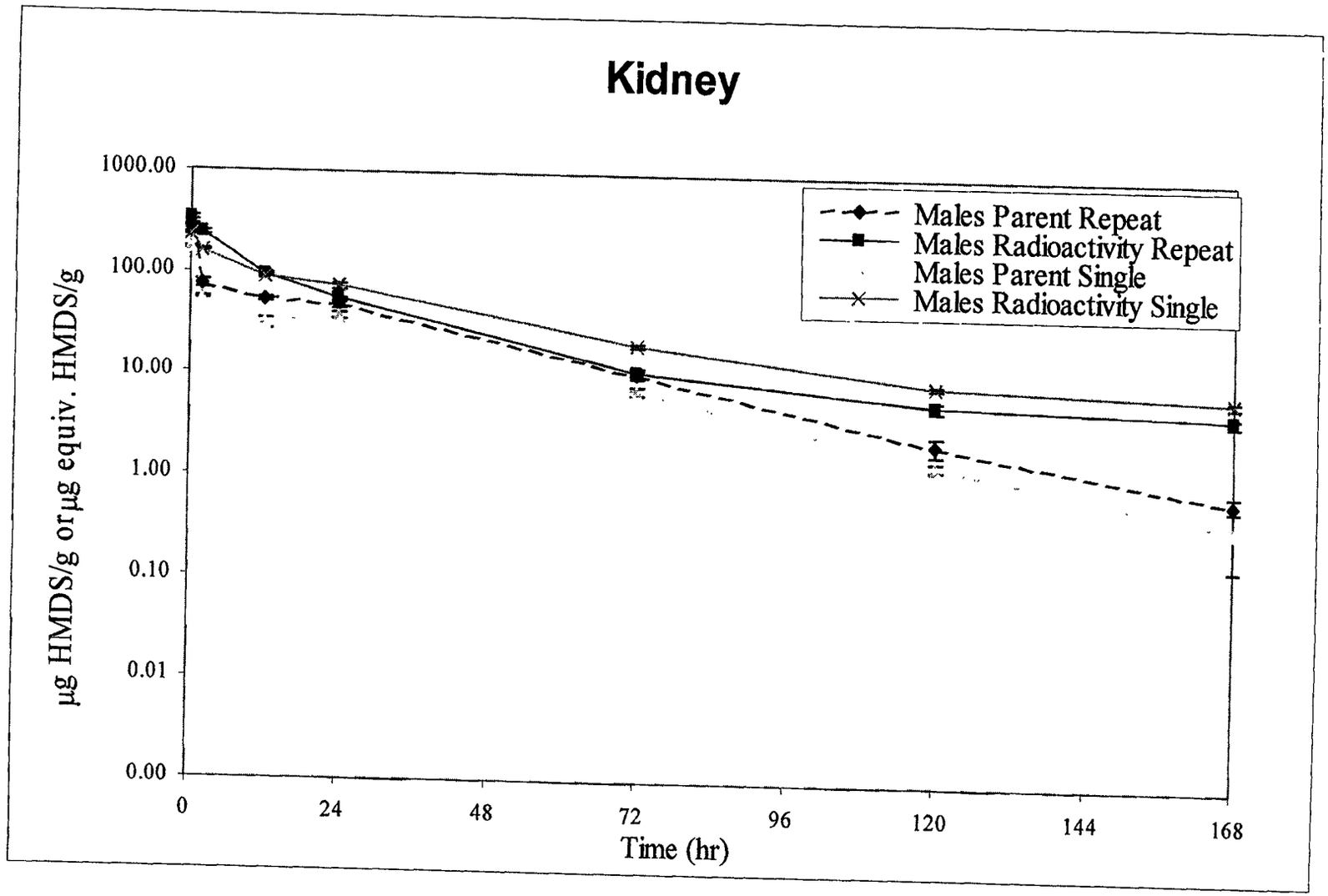


FIGURE 7 – Concentration of Parent HMDS and Radioactivity in Testes of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

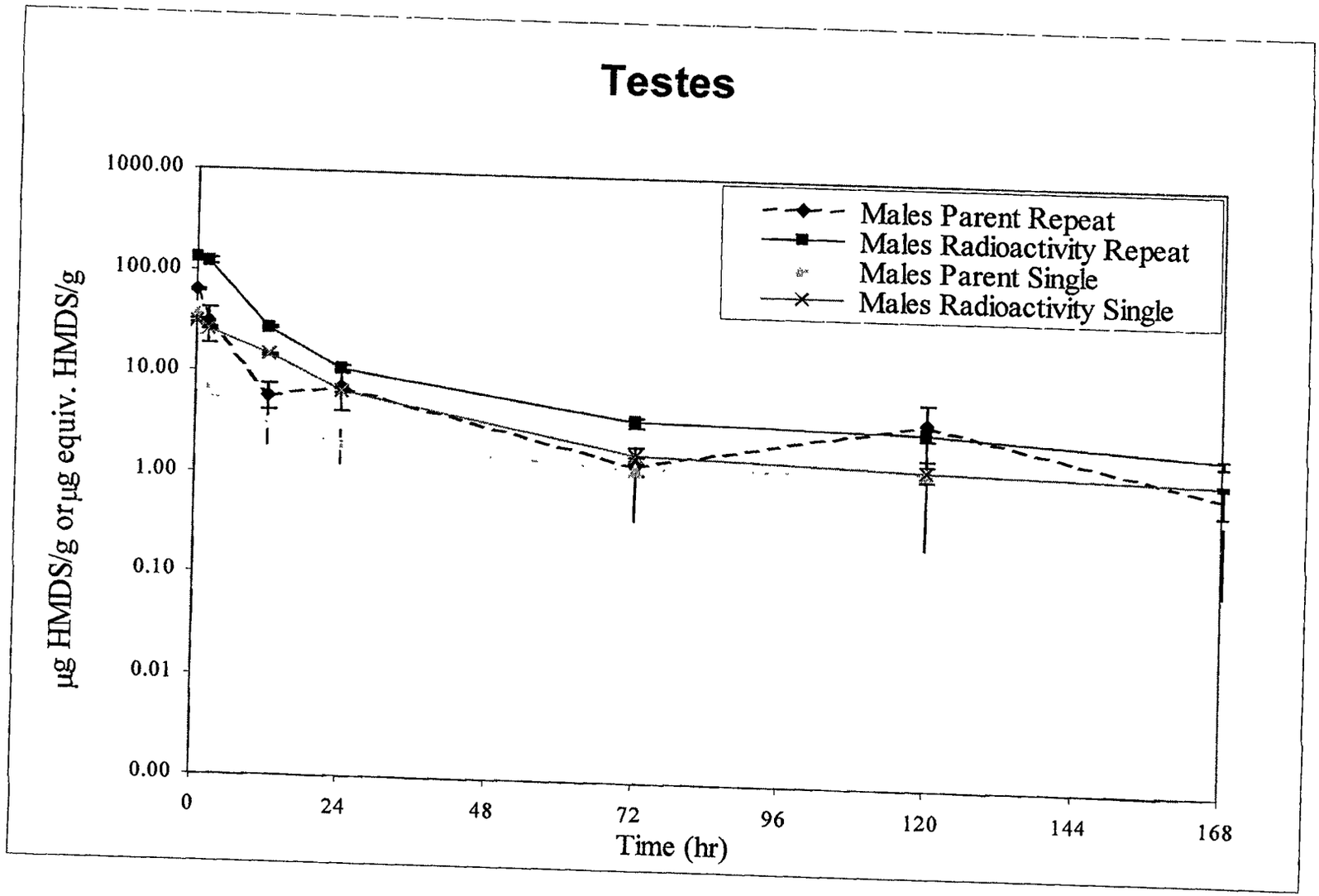


FIGURE 8 – Concentration of Parent HMDS and Radioactivity in Liver of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

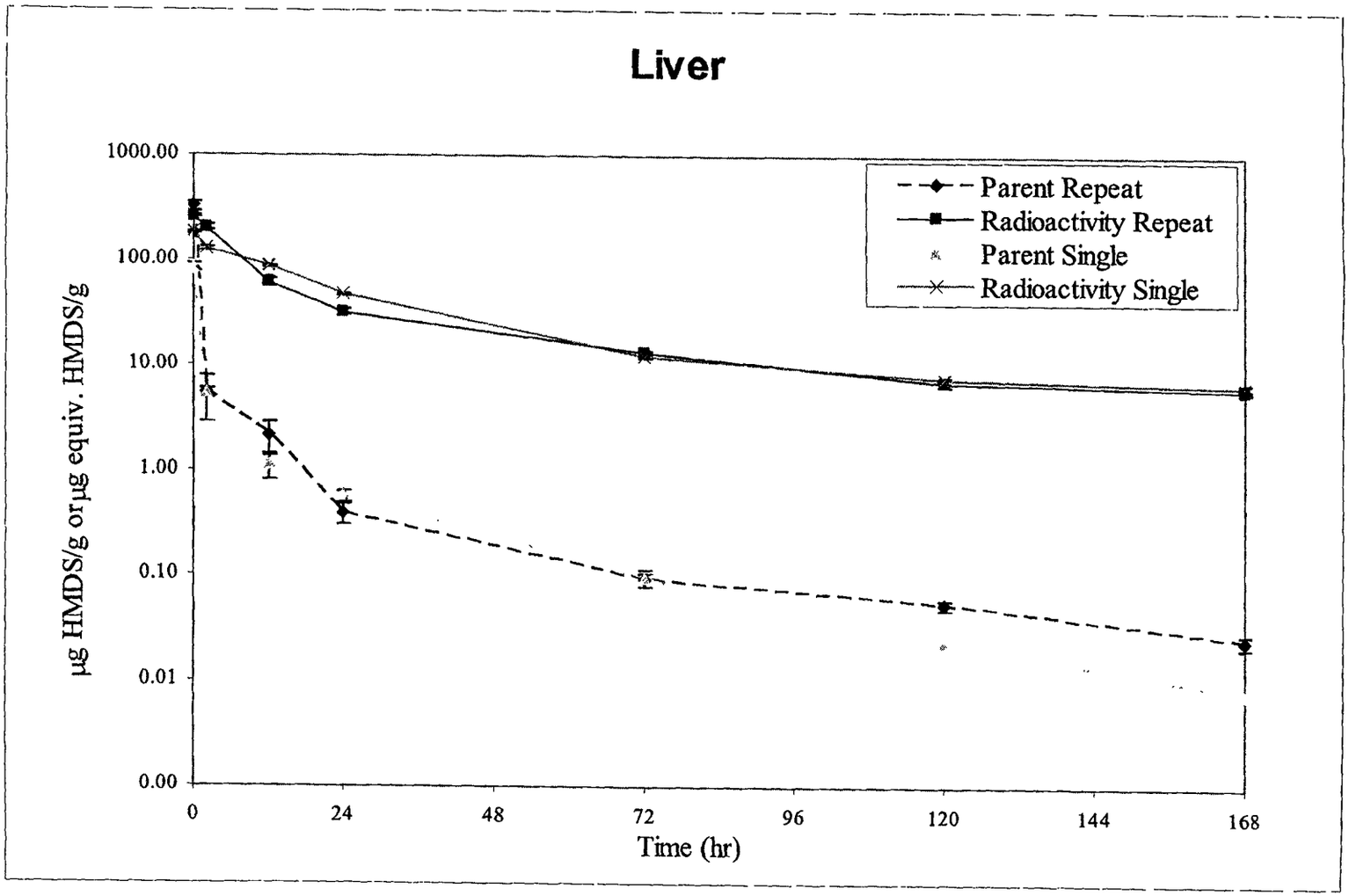


FIGURE 9 – Concentration of Parent HMDS and Radioactivity in Lung of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

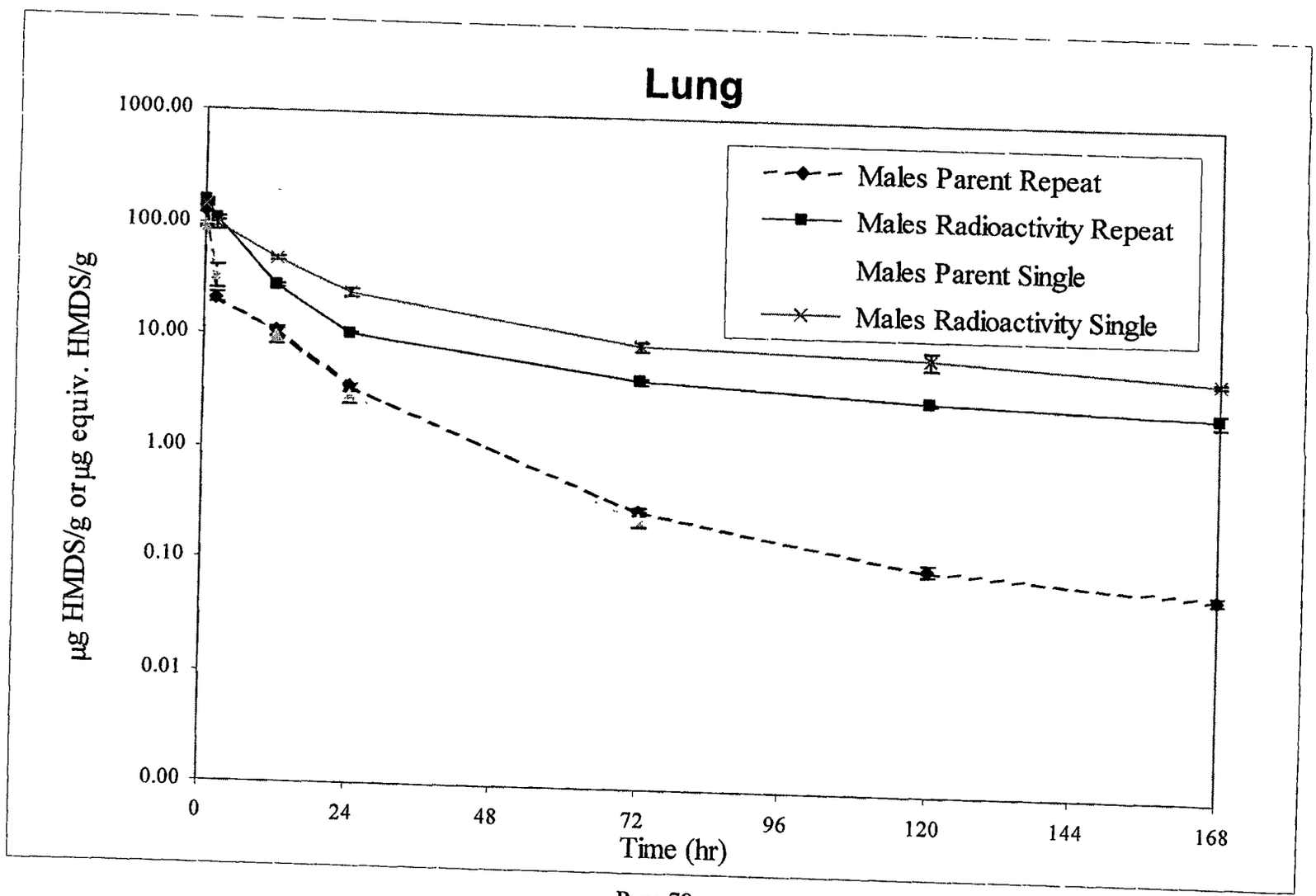


FIGURE 10 – Concentration of Parent HMDS and Radioactivity in Fat of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

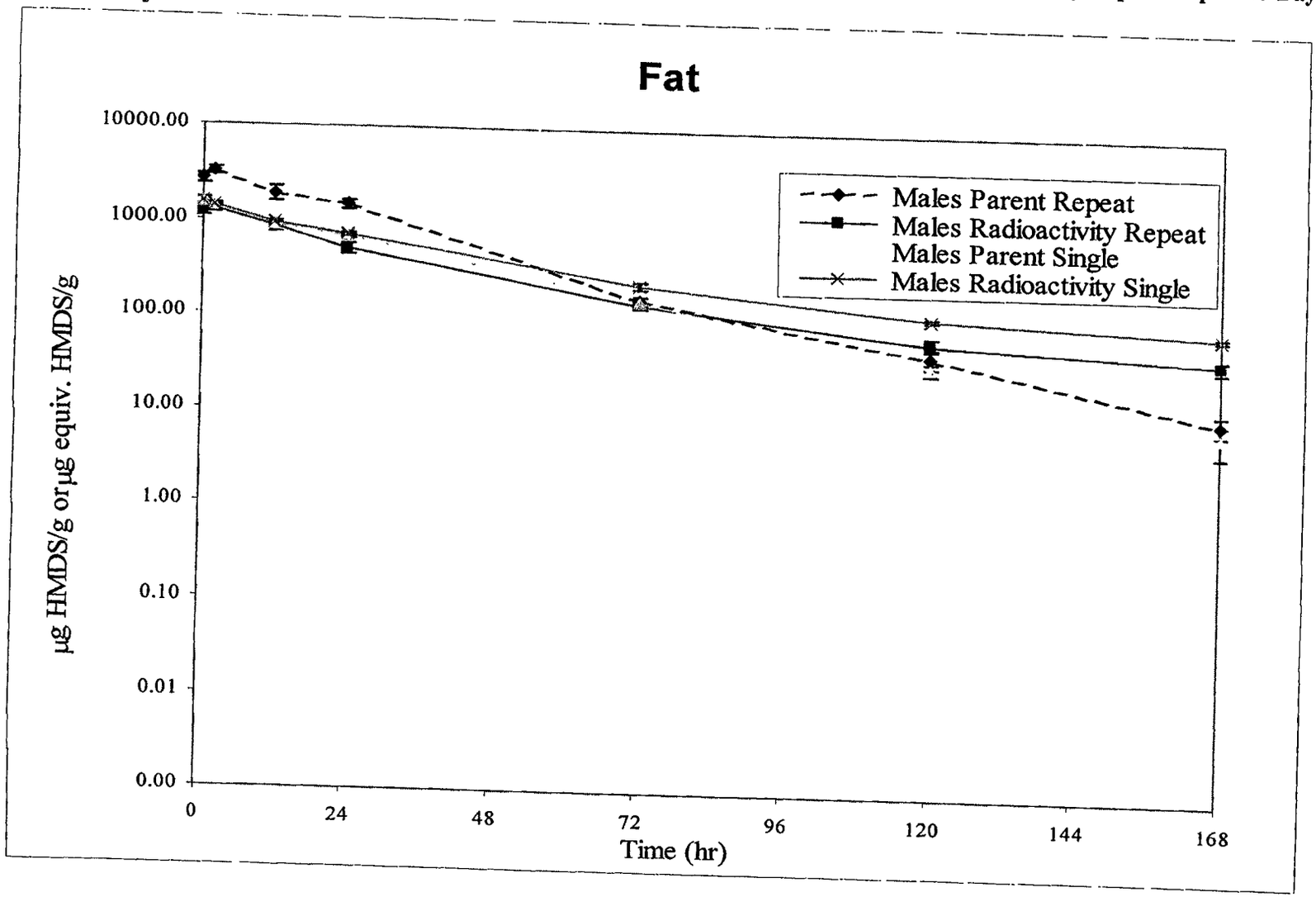


FIGURE 11 – Concentration of Parent HMDS and Radioactivity in Expired Volatiles of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

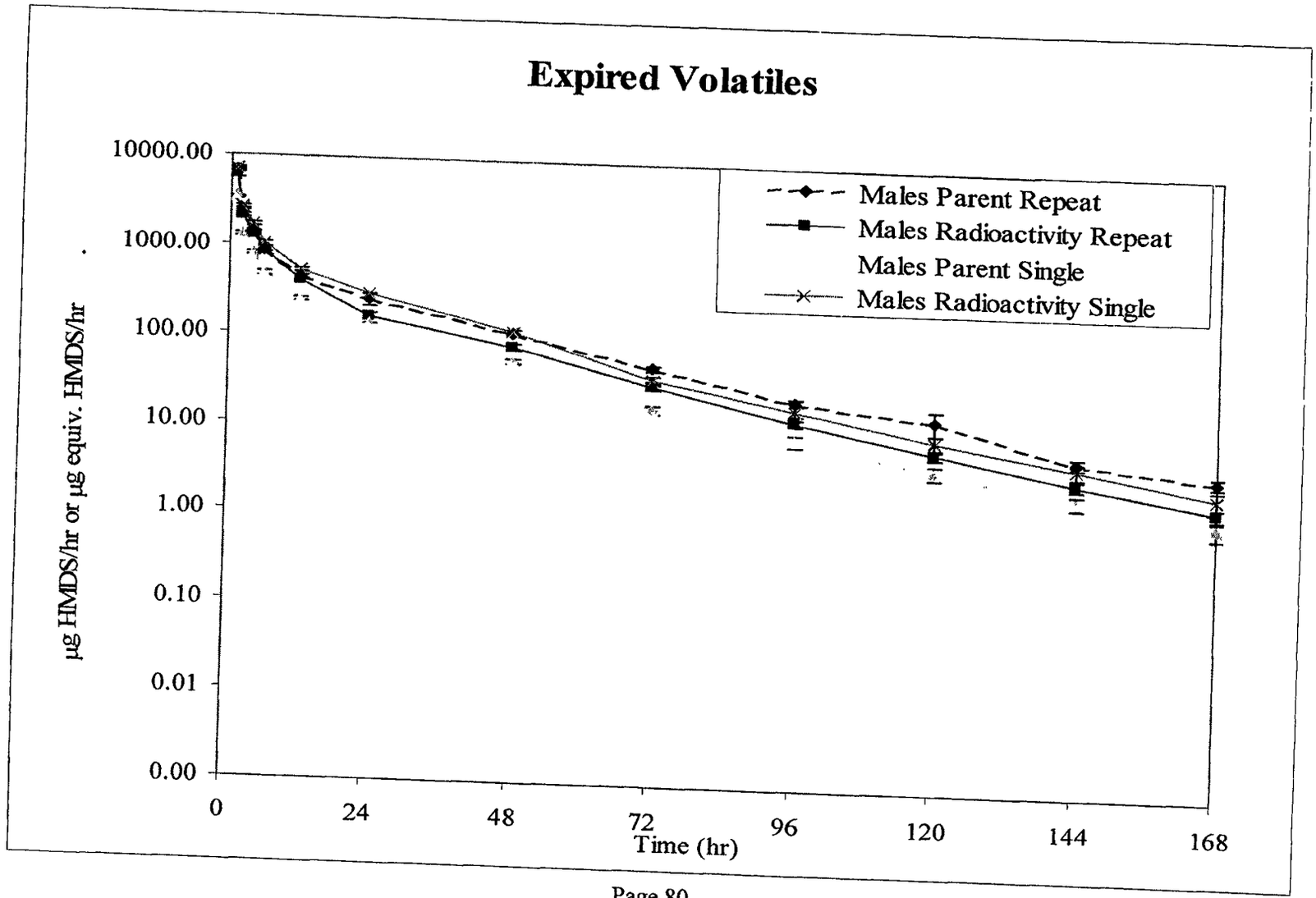


FIGURE 12 – Concentration of Radioactivity in Urine of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

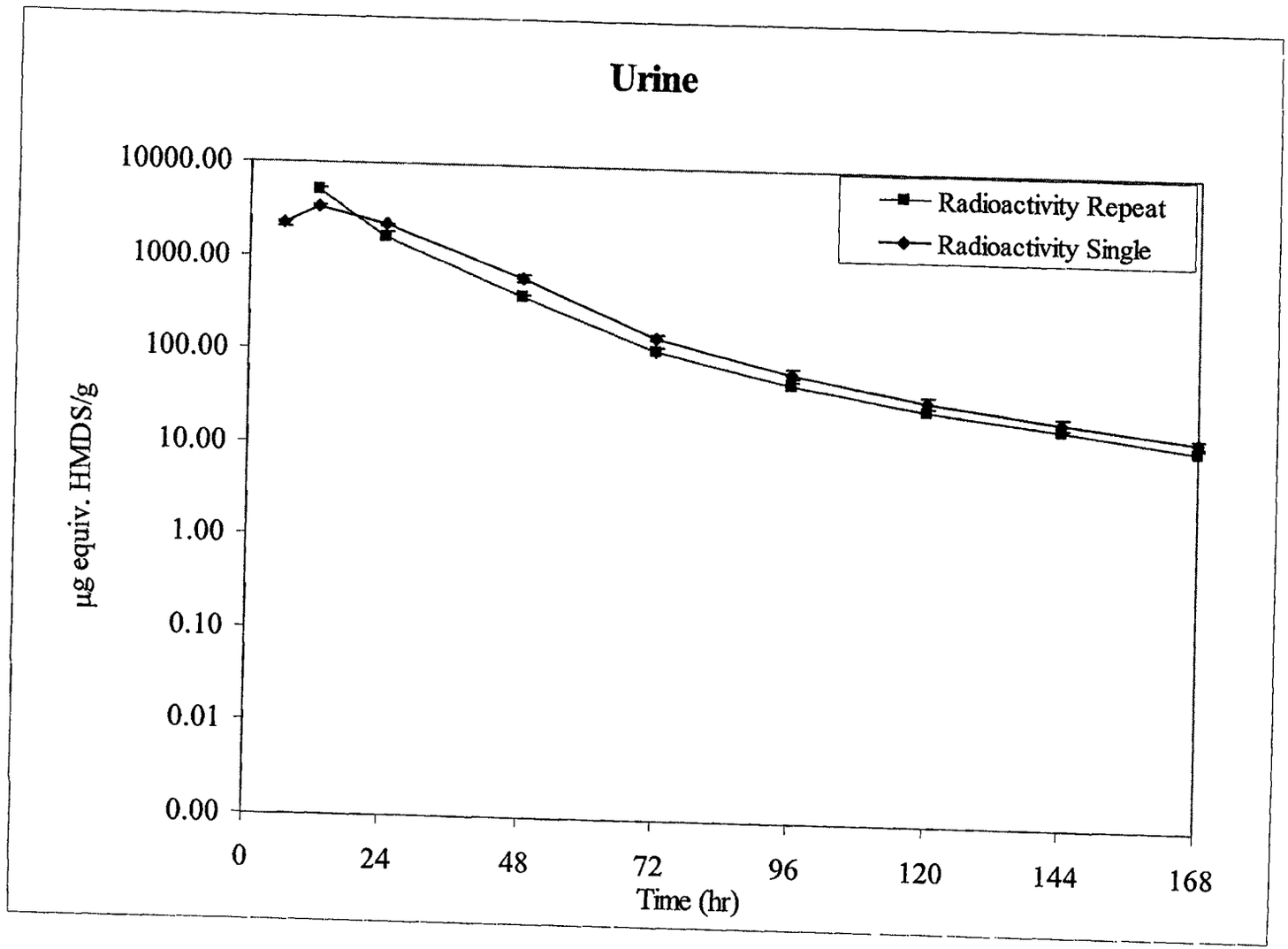


FIGURE 13 – Concentration of Radioactivity in Feces of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

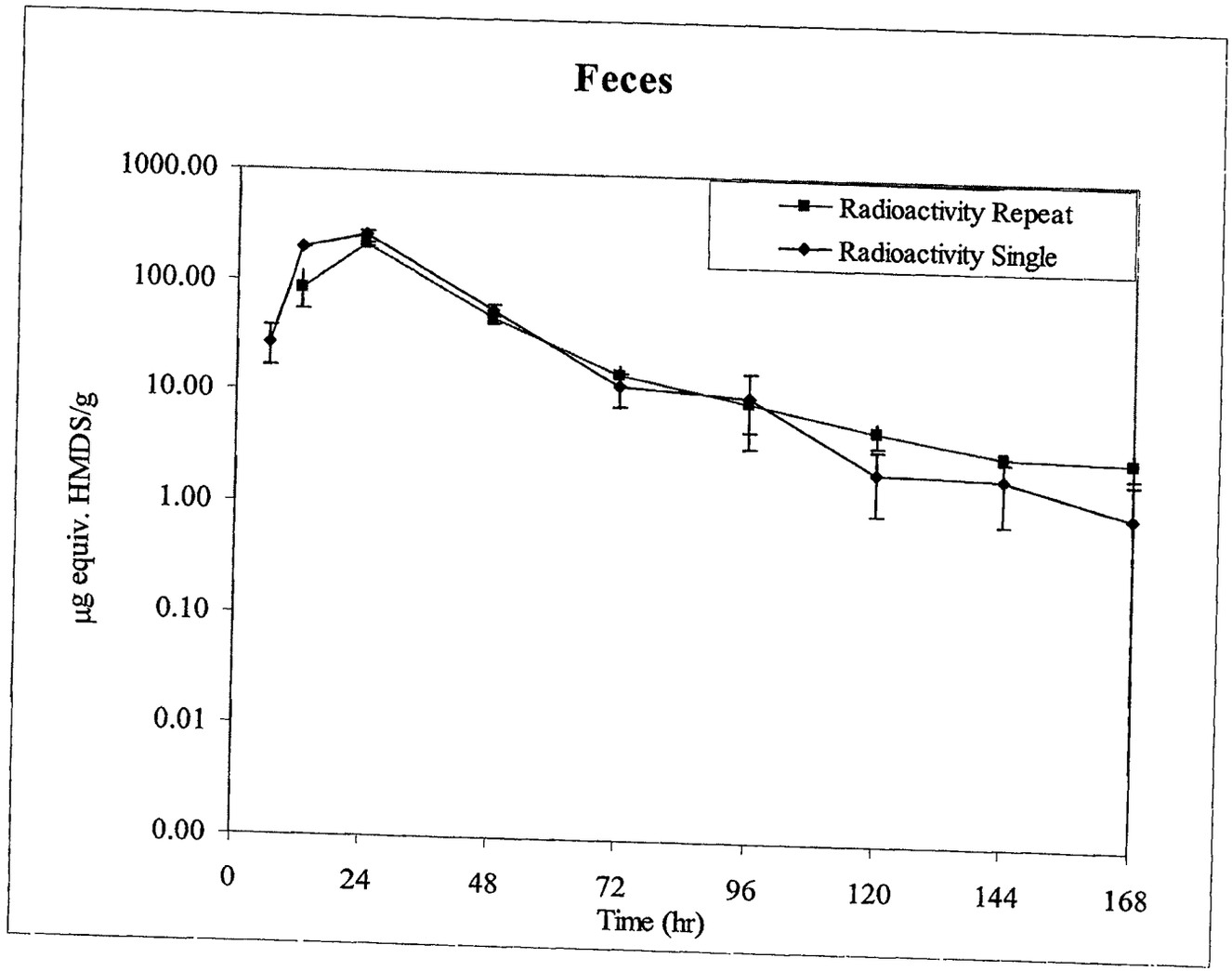


FIGURE 14 – Concentration of Radioactivity in CO_2 of Male Fischer 344 Rats Following Repeat Exposure Day 15 and Single Exposure Day 1

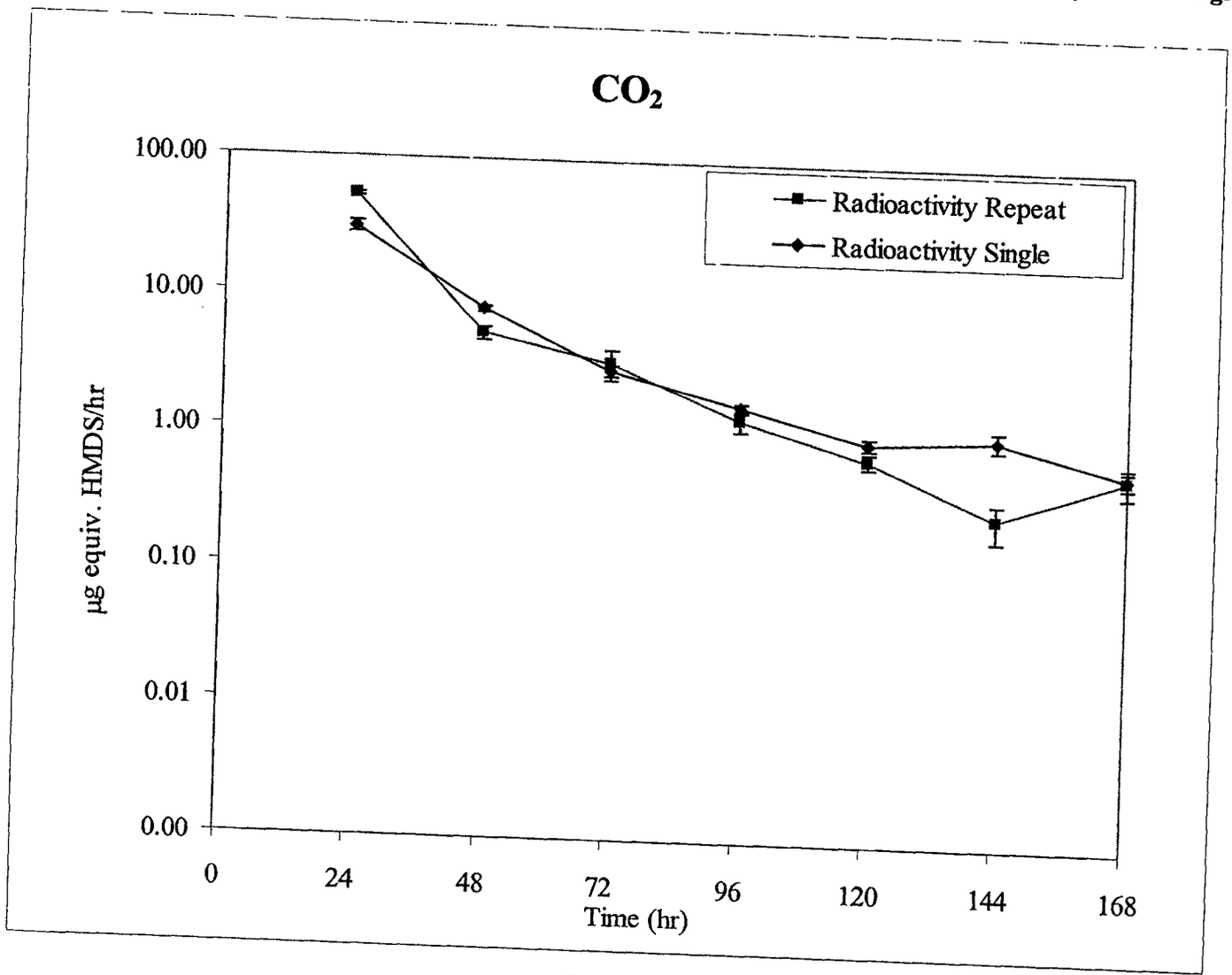
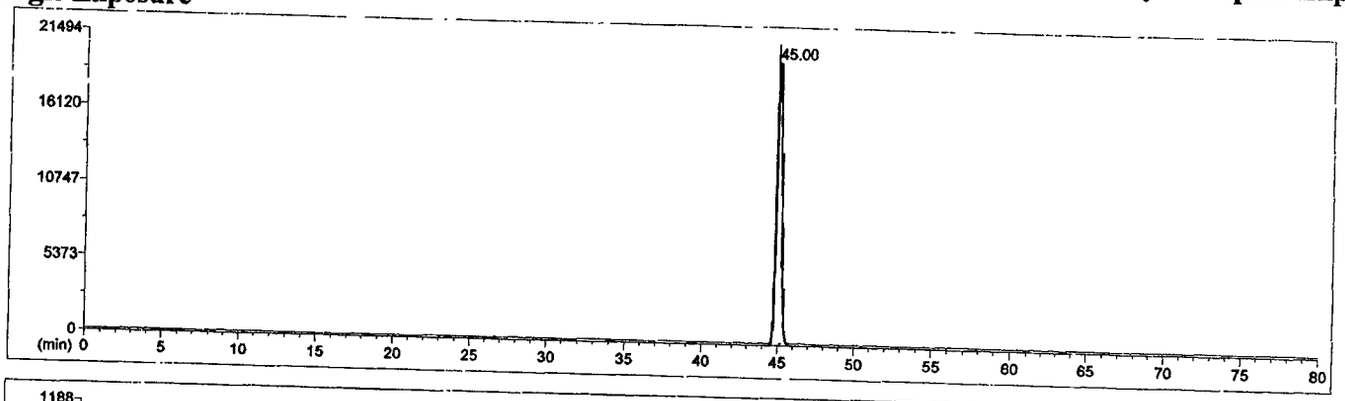
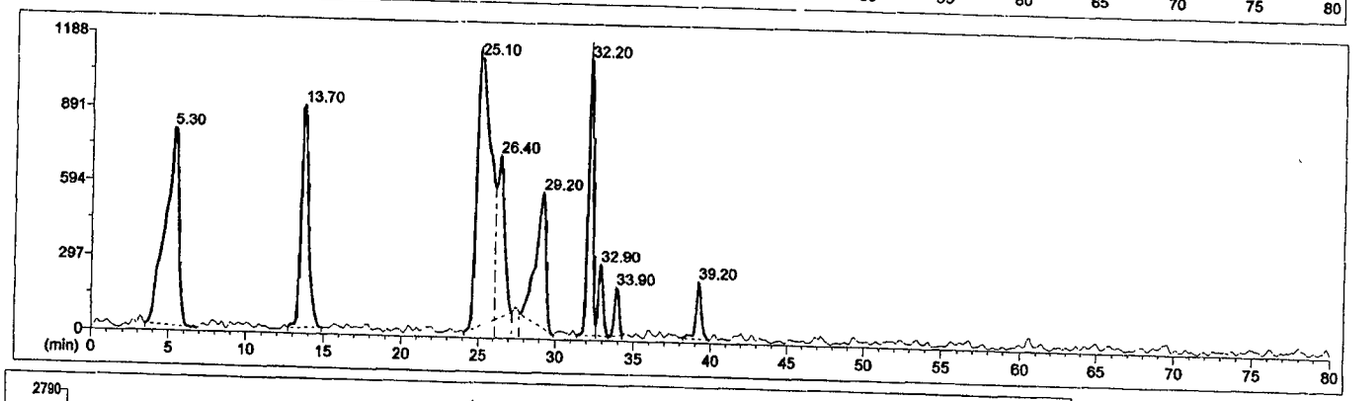


FIGURE 15 – Representative Chromatograms of a) ^{14}C-HMDS Solvent Standard b) 12 hour Urine Analysis Repeat Exposure c) 12 hour Urine Analysis Single Exposure

a)



b)



c)

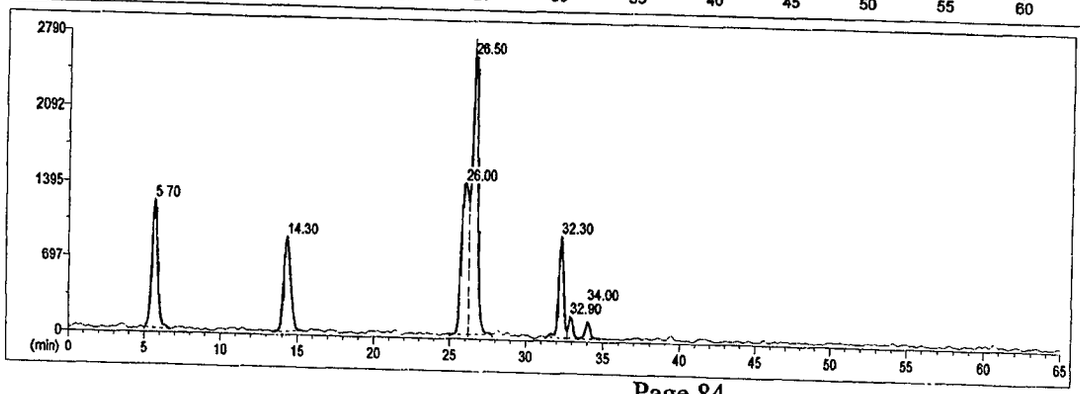


FIGURE 16 – Mass Balance as a Percent of the Body Burden Dose for Repeat and Single Exposure

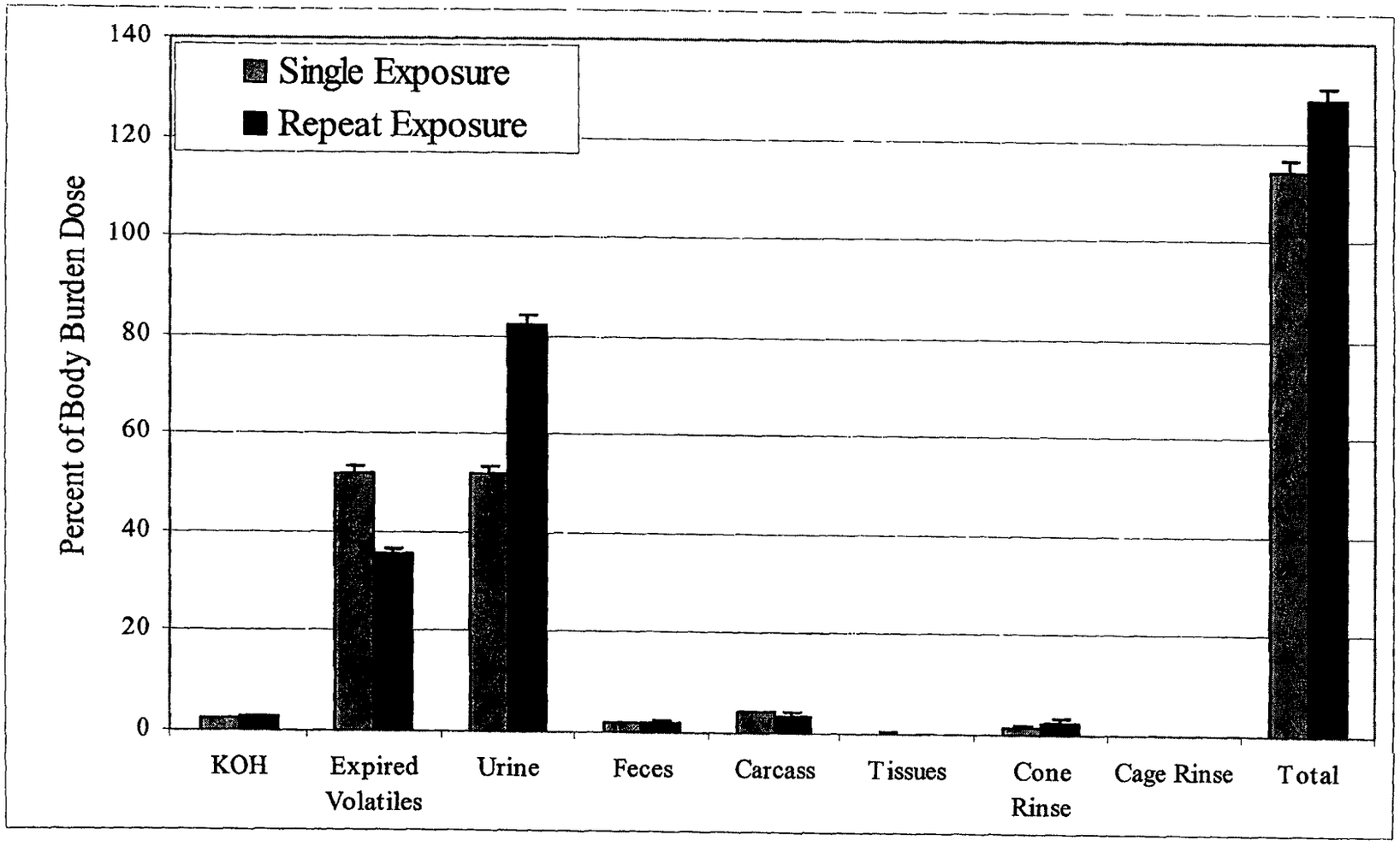
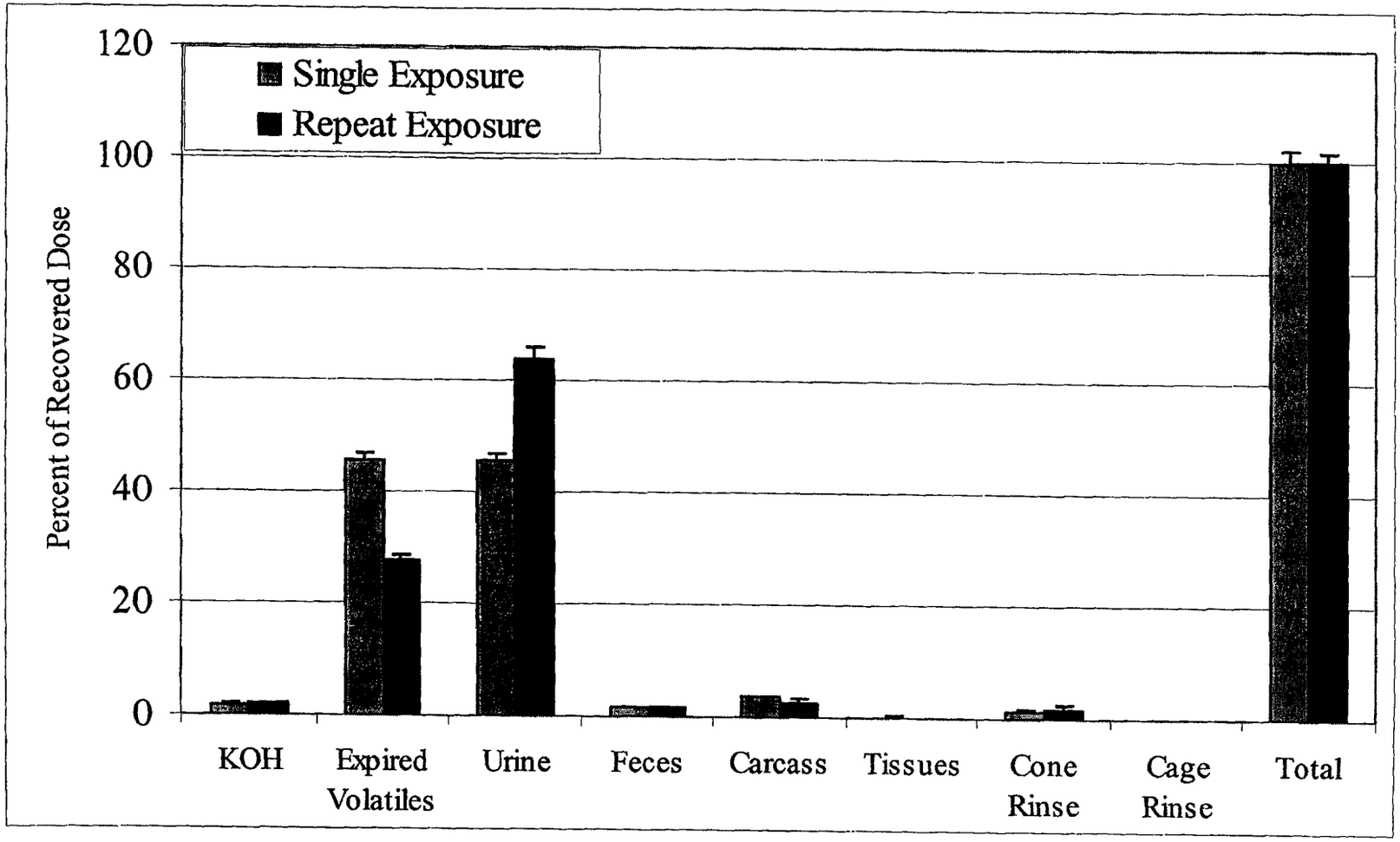


FIGURE 17 – Mass Balance as a Percent of the Total Recovered Dose for Repeat and Single Exposure



APPENDIX A - Inhalation Chamber Conditions during Nose-Only Exposures

Nose Only Chamber 1 (Day 1) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:44am	28.1	21.3	28.9
8:12am	28.1	21.7	28.3
8:33am	28.1	22.3	26.8
8:53am	28.1	22.5	26.0
9:15am	28.1	22.6	25.5
9:42am	28.1	22.9	25.9
10:12am	28.1	23.3	26.1
10:40am	28.1	23.8	24.4
11:06am	28.1	23.7	23.7
11:30am	28.1	24.1	22.5
11:55am	28.1	24.3	22.2
12:21pm	28.1	24.0	23.3
12:46pm	28.1	24.4	21.7
1:15pm	28.1	24.4	21.5
1:44pm	28.1	24.4	21.5
Mean	28.1	23.3	24.6
Std Dev	0.0	1.04	2.45
Max	28.1	24.4	28.9
Min	28.1	21.3	21.5

Nose Only Chamber 1 (Day 2) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:40am	28.1	20.6	30.1
8:05am	28.1	21.6	29.4
8:32am	28.1	22.2	27.5
8:58am	28.1	23.3	24.0
9:26am	28.1	23.5	23.7
9:52am	28.1	23.8	24.6
10:18am	28.1	24.0	24.1
10:48am	28.1	24.0	23.4
11:17am	28.1	24.0	22.9
11:44am	28.1	24.0	23.0
12:12pm	28.1	23.4	24.4
12:33pm	28.1	23.3	24.5
12:55pm	28.1	23.4	24.9
1:17pm	28.1	23.5	26.4
1:41pm	28.1	23.7	25.9
Mean	28.1	23.2	25.3
Std Dev	0.0	0.99	2.21
Max	28.1	24.0	30.1
Min	28.1	20.6	22.9

Nose Only Chamber 1 (Day 3) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:36am	28.1	21.1	32.1
8:06am	28.1	21.8	30.1
8:32am	28.1	22.3	28.3
8:59am	28.1	22.6	26.8
9:25am	28.1	22.9	27.8
9:52am	28.1	23.0	26.9
10:19am	28.1	23.0	26.6
10:47am	28.1	22.9	26.1
11:12am	28.1	23.0	25.7
11:42am	28.1	23.2	25.4
12:10pm	28.1	23.0	25.9
12:38pm	28.1	23.1	25.7
1:05pm	28.1	23.3	26.0
1:33pm	28.1	23.7	25.9
Mean	28.1	22.8	27.1
Std Dev	0.0	0.66	1.93
Max	28.1	23.7	32.1
Min	28.1	21.1	25.4

Nose Only Chamber 1 (Day 4) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:37am	28.1	21.6	31.0
8:00am	28.1	21.9	30.5
8:27am	28.1	22.4	28.4
8:55am	28.1	22.7	26.7
9:25am	28.1	23.0	25.4
9:53am	28.1	23.0	25.6
10:21am	28.1	23.1	25.7
10:49am	28.1	23.6	26.4
11:18am	28.1	23.9	24.6
11:47am	28.1	23.9	24.0
12:16pm	28.1	23.9	24.3
12:38pm	28.1	23.8	24.1
1:04pm	28.1	23.6	24.6
1:18pm	28.1	23.8	24.3
1:38pm	28.1	23.9	25.0
Mean	28.1	23.2	26.0
Std Dev	0.0	0.77	2.24
Max	28.1	23.9	31.0
Min	28.1	21.6	24.0

Nose Only Chamber 1 (Day 5) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:20am	28.1	21.2	32.8
7:47am	28.1	22.2	28.8
8:17am	28.1	23.0	25.7
8:43am	28.1	23.1	25.0
9:10am	28.1	23.4	24.6
9:39am	28.1	23.4	24.3
10:03am	28.1	23.6	26.6
10:32am	28.1	23.9	24.9
10:59am	28.1	23.8	25.0
11:23am	28.1	23.8	25.3
12:00pm	28.1	23.3	26.4
12:23pm	28.1	23.6	24.0
12:51pm	28.1	23.8	24.5
1:12pm	28.1	23.6	26.4
Mean	28.1	23.3	26.0
Std Dev	0.0	0.74	2.31
Max	28.1	23.9	32.8
Min	28.1	21.2	24.0

Nose Only Chamber 1 (Day 6) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
8:16am	28.7	21.5	31.5
8:45am	28.7	23.3	26.8
9:15am	28.7	23.9	22.9
9:45am	28.7	24.4	24.3
10:15am	28.7	24.3	24.0
10:46am	28.7	24.2	22.0
11:15am	28.1	24.4	24.6
11:45am	28.1	24.1	22.3
12:15pm	27.5	24.3	23.6
12:45pm	28.1	24.0	24.0
1:15pm	28.1	23.7	22.5
1:45pm	28.1	23.4	24.3
Mean	28.4	23.8	24.4
Std Dev	0.40	0.81	2.58
Max	28.7	24.4	31.5
Min	27.5	21.5	22.0

Nose Only Chamber 1 (Day 7) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
8:12am	28.1	20.9	32.0
8:31am	28.1	21.3	29.3
8:56am	28.1	22.1	28.6
9:26am	28.1	22.5	26.6
9:53am	28.1	22.5	25.9
10:20am	28.1	22.9	26.6
10:48am	28.1	23.0	24.1
11:15am	28.1	23.4	25.0
11:44am	28.1	23.6	23.5
12:08pm	28.1	23.6	23.3
12:33pm	28.1	23.6	24.7
12:53pm	28.1	23.2	24.4
1:19pm	28.1	23.1	24.6
1:46pm	28.1	22.9	25.0
2:10pm	28.1	23.3	25.3
Mean	28.1	22.8	25.9
Std Dev	0.0	0.82	2.39
Max	28.1	23.6	32.0
Min	28.1	20.9	23.3

Nose Only Chamber 1 (Day 8) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:31am	28.1	21.5	30.3
7:59am	28.1	22.2	28.6
8:25am	28.1	22.5	27.0
8:54am	28.1	22.6	26.2
9:24am	28.1	22.9	26.0
9:50am	28.1	23.0	27.1
10:19am	28.1	23.0	26.0
10:46am	28.1	23.0	26.2
11:10am	28.1	23.0	26.1
11:38am	28.1	23.5	26.6
12:06pm	28.1	23.5	24.3
12:34pm	28.1	24.0	24.6
1:02pm	28.1	24.0	24.0
1:22pm	28.1	24.0	23.6
1:45pm	28.1	23.4	26.2
Mean	28.1	23.1	26.2
Std Dev	0.0	0.70	1.73
Max	28.1	24.0	30.3
Min	28.1	21.5	23.6

Nose Only Chamber 1 (Day 9) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:37am	28.1	21.4	31.0
8:03am	28.1	22.1	29.5
8:30am	28.1	22.3	27.9
8:57am	28.1	22.7	27.6
9:25am	28.1	22.9	26.7
9:54am	28.1	23.0	25.7
10:20am	28.1	23.0	25.3
10:47am	28.1	23.0	26.3
11:04am	28.1	23.0	25.1
11:30am	28.1	23.1	26.1
11:59am	28.1	22.9	24.8
12:25pm	28.1	23.0	26.2
12:56pm	28.1	22.7	25.0
1:24pm	28.1	22.9	25.0
Mean	28.1	22.7	26.6
Std Dev	0.0	0.48	1.84
Max	28.1	23.1	31.0
Min	28.1	21.4	24.8

Nose Only Chamber 1 (Day 10) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:39am	28.1	21.0	31.5
8:03am	28.1	21.8	28.6
8:26am	28.1	22.3	28.7
8:55am	28.1	22.5	27.0
9:24am	28.1	22.6	24.2
10:am	28.1	22.0	24.4
10:20am	28.1	22.2	25.6
10:45am	28.1	22.9	26.6
11:09am	28.1	23.0	27.6
11:33am	28.1	23.0	25.8
12:03pm	28.1	23.1	26.2
12:27pm	28.1	23.0	26.2
12:49pm	28.1	22.9	27.0
1:13pm	28.1	23.0	27.9
1:36pm	28.1	23.1	26.4
Mean	28.1	22.6	26.9
Std Dev	0.0	0.60	1.82
Max	28.1	23.1	31.5
Min	28.1	21.0	24.2

Nose Only Chamber 1 (Day11) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:42am	28.1	21.4	31.1
8:08am	28.1	22.2	30.6
8:31am	28.1	22.3	28
8:56am	28.1	22.3	27.3
9:21am	28.1	22.4	26.8
9:47am	28.1	22.3	26
10:17am	28.1	22.6	27.2
10:41am	28.1	22.5	25.7
11:10am	28.1	22.3	26.1
11:40am	28.1	22.7	27.3
12:10pm	28.1	22.8	27.7
12:33pm	28.1	23.0	27.1
1:02pm	28.1	22.6	26.1
1:19pm	28.1	22.9	27.6
1:41pm	28.1	22.9	26.7
Mean	28.1	22.5	27.4
Std Dev	0.0	0.39	1.55
Max	28.1	23.0	31.1
Min	28.1	21.4	25.7

Nose Only Chamber 1 (Day 12) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:37am	28.1	21.2	31.2
7:56am	28.1	21.5	29.1
8:26am	28.1	21.5	28.1
8:56am	28.1	22.0	26.2
9:22am	28.1	22.4	27.9
9:49am	28.1	22.4	26.6
10:15am	28.1	22.6	27.7
10:41am	28.1	22.5	25.7
11:08am	28.1	22.6	25.9
11:29am	28.1	22.6	25.0
11:56am	28.1	22.8	26.6
12:24pm	28.1	22.8	26.0
12:50pm	28.1	22.4	24.2
1:12pm	28.1	22.2	23.9
1:38pm	28.1	22.3	25.9
Mean	28.1	22.3	26.7
Std Dev	0.0	0.49	1.90
Max	28.1	22.8	31.2
Min	28.1	21.2	23.9

Nose Only Chamber 1 (Day13) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:26am	28.1	20.9	32.1
7:50am	28.1	21.5	30.8
8:17am	28.1	21.9	28.5
8:45am	28.1	21.9	26.4
9:12am	28.1	22.4	28.1
9:42am	28.1	22.1	27.0
10:11am	28.1	22.4	27.0
10:35am	28.1	22.4	27.0
11:03am	28.1	22.5	26.7
11:27am	28.1	22.6	27.3
11:53am	28.1	22.7	25.7
12:19pm	28.1	23.6	24.9
12:48pm	28.1	22.9	25.1
1:15pm	28.1	22.9	27.1
1:29pm	28.1	23.0	25.7
Mean	28.1	22.4	27.3
Std Dev	0.0	0.66	1.97
Max	28.1	23.6	32.1
Min	28.1	20.9	24.9

Nose Only Chamber 1 (Day 14) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:43am	27.5	21.4	31.0
8:10am	28.1	22.6	26.1
8:40am	28.1	21.6	24.7
9:10am	28.1	22.1	28.3
9:40am	28.1	22.2	27.3
10:10am	28.1	22.3	27.4
10:40am	28.1	22.5	27.3
11:10am	28.1	22.7	23.7
11:37am	28.1	22.4	23.1
12:09pm	28.1	22.0	25.0
12:39pm	28.1	21.9	25.3
1:08pm	28.1	22.0	25.3
1:20pm	28.1	22.1	25.4
Mean	28.1	22.1	26.1
Std Dev	0.17	0.38	2.10
Max	28.1	22.7	31.0
Min	27.5	21.4	23.1

Nose Only Chamber 1 (Day 15) Repeat Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:58am	28.1	21.0	30.0
8:21am	28.1	21.1	29.6
8:45am	28.1	21.0	28.9
9:11am	28.1	21.2	28.5
9:37am	28.1	21.5	26.9
10:06am	28.1	21.6	25.9
10:34am	28.1	21.8	24.9
10:56am	28.1	21.9	24.7
11:21am	28.1	21.9	24.6
11:44am	28.1	22.5	28.8
12:10pm	28.1	22.5	26.0
12:35pm	28.1	22.4	25.4
12:52pm	28.1	22.4	24.6
1:18pm	28.1	22.2	25.4
1:44pm	28.1	22.3	27.5
2:10pm	28.1	22.5	26.4
2:38pm	28.1	22.2	25.0
3:04pm	28.1	22.7	27.0
3:33pm	28.1	22.2	26.6
Mean	28.1	21.9	26.7
Std Dev	0.0	0.56	1.77
Max	28.1	22.7	30.0
Min	28.1	21.0	24.6

Nose Only Chamber 1 (Day 1) Single Exposure			
Time	Air Flow (LPM)	Temperature (°C)	Humidity (%RH)
7:57am	28.0	22.4	32.3
8:26am	28.0	22.4	30.9
8:56am	28.0	22.2	30.6
9:26am	28.0	22.4	30.2
9:56am	28.0	22.8	28.9
10:25am	28.0	23.1	27.4
10:55am	28.0	23.3	27.1
11:22am	28.0	23.5	27.1
11:52am	28.0	23.5	27.8
12:23pm	28.0	23.5	27.7
12:51pm	28.0	23.6	26.9
1:21pm	28.0	23.9	25.7
1:51pm	28.0	23.9	26.4
2:21pm	28.0	23.7	27.4
2:51pm	28.0	23.7	27.0
3:21pm	28.0	23.4	27.3
3:48pm	28.0	23.4	28.2
Mean	28.0	23.2	28.2
Std Dev	0.0	0.56	1.80
Max	28.0	23.9	32.3
Min	28.0	22.2	25.7

APPENDIX B - Individual Measured Chamber Concentrations during Nose-Only Exposure

Exposure Day 1 6-2-03

6-2-03 exposure	area counts	ppm	mg/L
.run	414901	**5115**	**33.68**
001.run	405144	**4988**	**32.85**
002.run	410496	**5058**	**33.31**
003.run	410119	**5053**	**33.27**
004.run	406113	**5001**	**32.93**
005.run	411388	**5069**	**33.38**
006.run	407754	**5022**	**33.07**
007.run	411640	**5072**	**33.40**
008.run	407584	**5020**	**33.06**
009.run	404947	**4985**	**32.83**
010.run	401679	**4943**	**32.55**
011.run	422110	**5208**	**34.30**
012.run	417269	**5146**	**33.89**
013.run	414751	**5113**	**33.67**
014.run	400171	**4923**	**32.42**
015.run	408360	**5030**	**33.12**
016.run	421807	**5205**	**34.27**
017.run	394505	**4850**	**31.94**
018.run	402672	**4956**	**32.64**
019.run	404975	**4986**	**32.83**
Mean:		5037	33.17
S.D.		90.9	0.599

Exposure Day 2 6-3-03

6-3-03 exposure	area counts	ppm	mg/L
.run	415804	**5126**	**33.76**
001.run	417504	**5149**	**33.91**
002.run	417631	**5150**	**33.92**
003.run	414438	**5109**	**33.64**
004.run	417720	**5151**	**33.92**
005.run	418501	**5162**	**33.99**
006.run	409296	**5042**	**33.20**
007.run	418715	**5164**	**34.01**
008.run	416850	**5140**	**33.85**
009.run	418474	**5161**	**33.99**
010.run	412321	**5081**	**33.46**
011.run	415050	**5117**	**33.70**
012.run	408719	**5034**	**33.15**
013.run	418534	**5162**	**33.99**
014.run	413392	**5095**	**33.55**
015.run	420185	**5183**	**34.13**
016.run	399559	**4915**	**32.37**
017.run	412796	**5087**	**33.50**
018.run	415926	**5128**	**33.77**
Mean:		5114	33.67
S.D.		63.4	0.417

Exposure Day 3 6-4-03

6-4-03 exposures	area counts	ppm	mg/L
.run	415586	**5124**	**33.74**
001.run	414052	**5104**	**33.61**
002.run	416759	**5139**	**33.84**
003.run	418018	**5155**	**33.95**
004.run	410269	**5055**	**33.29**
005.run	418453	**5161**	**33.99**
006.run	404008	**4973**	**32.75**
007.run	406386	**5004**	**32.95**
008.run	408394	**5030**	**33.13**
009.run	415927	**5128**	**33.77**
010.run	413607	**5098**	**33.57**
011.run	427994	**5285**	**34.80**
012.run	411168	**5066**	**33.36**
013.run	419494	**5174**	**34.08**
014.run	418989	**5168**	**34.03**
015.run	405864	**4997**	**32.91**
016.run	407013	**5012**	**33.01**
017.run	409635	**5046**	**33.23**
Mean:		5096	33.56
S.D.		79.8	0.525

Exposure Day 4 6-5-03

6-5-03 exposures	area counts	ppm	mg/L
.run	407764	**5022**	**33.07**
001.run	410617	**5059**	**33.32**
002.run	413365	**5095**	**33.55**
003.run	416417	**5134**	**33.81**
004.run	410136	**5053**	**33.27**
005.run	407319	**5016**	**33.03**
006.run	412111	**5078**	**33.44**
007.run	425681	**5255**	**34.61**
008.run	413514	**5097**	**33.56**
009.run	406272	**5003**	**32.94**
010.run	407833	**5023**	**33.08**
011.run	388378	**4770**	**31.41**
012.run	407941	**5024**	**33.09**
013.run	406834	**5010**	**32.99**
014.run	414918	**5115**	**33.68**
015.run	412029	**5077**	**33.44**
016.run	407510	**5019**	**33.05**
017.run	415625	**5124**	**33.74**
018.run	398529	**4902**	**32.28**
Mean:		5046	33.23
S.D.		98.0	0.645

Exposure Day 5 6-6-03

6-6-03 exposure	area counts	ppm	mg/L
.run	407121	**5014**	**33.02**
001.run	401212	**4937**	**32.51**
002.run	411052	**5065**	**33.35**
003.run	408342	**5030**	**33.12**
004.run	408951	**5037**	**33.17**
005.run	409028	**5038**	**33.18**
006.run	408277	**5029**	**33.12**
007.run	408413	**5030**	**33.13**
008.run	408126	**5027**	**33.10**
009.run	407907	**5024**	**33.08**
010.run	404949	**4985**	**32.83**
011.run	429146	**5300**	**34.90**
012.run	410755	**5061**	**33.33**
013.run	407985	**5025**	**33.09**
014.run	411878	**5075**	**33.42**
015.run	418778	**5165**	**34.01**
016.run	413437	**5096**	**33.56**
017.run	409922	**5050**	**33.26**
018.run	411144	**5066**	**33.36**
Mean:		5055	33.29
S.D.		74.6	0.491

Exposure Day 6 6-7-03

`6-7-03	area counts	ppm	mg/L
.run	399875	**4919**	**32.40**
001.run	405182	**4988**	**32.85**
002.run	398024	**4895**	**32.24**
003.run	404517	**4980**	**32.79**
004.run	402771	**4957**	**32.64**
005.run	383901	**4712**	**31.03**
006.run	377146	**4624**	**30.45**
007.run	384992	**4726**	**31.12**
008.run	389708	**4787**	**31.53**
009.run	394419	**4849**	**31.93**
010.run	398016	**4895**	**32.24**
011.run	393966	**4843**	**31.89**
012.run	389482	**4784**	**31.51**
013.run	383524	**4707**	**31.00**
Mean:		4833	31.83
S.D.		113.3	0.746

Exposure Day 7 6-8-03

6-8-03 exposure	area counts	ppm	mg/L
.run	390209	**4794**	**31.57**
001.run	396836	**4880**	**32.14**
002.run	405137	**4988**	**32.85**
003.run	395261	**4859**	**32.00**
004.run	396991	**4882**	**32.15**
005.run	393829	**4841**	**31.88**
006.run	393009	**4830**	**31.81**
007.run	411735	**5074**	**33.41**
008.run	398473	**4901**	**32.28**
009.run	406625	**5007**	**32.97**
010.run	400132	**4923**	**32.42**
011.run	394510	**4850**	**31.94**
012.run	396357	**4874**	**32.10**
013.run	391327	**4808**	**31.66**
014.run	397741	**4892**	**32.21**
Mean:		4893	32.23
S.D.		77.0	0.507

Exposure Day 8 6-9-03

6-9-03 exposure	area counts	ppm	mg/L
.run	400954	**4933**	**32.49**
001.run	391826	**4815**	**31.71**
002.run	402703	**4956**	**32.64**
003.run	398991	**4908**	**32.32**
004.run	390538	**4798**	**31.60**
005.run	406519	**5006**	**32.97**
006.run	404296	**4977**	**32.77**
007.run	406141	**5001**	**32.93**
008.run	390141	**4793**	**31.56**
009.run	401682	**4943**	**32.55**
010.run	414222	**5106**	**33.62**
011.run	400932	**4933**	**32.49**
012.run	399242	**4911**	**32.34**
013.run	404027	**4973**	**32.75**
014.run	397309	**4886**	**32.18**
015.run	405750	**4996**	**32.90**
016.run	390735	**4801**	**31.61**
Mean:		4926	32.44
S.D.		86.5	0.569

Exposure Day 9 6-10-03

6-10-03 exposure	area counts	ppm	mg/L
.run	398812	**4906**	**32.31**
001.run	406572	**5006**	**32.97**
002.run	396192	**4872**	**32.08**
003.run	395030	**4856**	**31.98**
004.run	400797	**4931**	**32.48**
005.run	401863	**4945**	**32.57**
006.run	409277	**5042**	**33.20**
007.run	408099	**5026**	**33.10**
008.run	405208	**4989**	**32.85**
009.run	401314	**4938**	**32.52**
010.run	412658	**5086**	**33.49**
011.run	398505	**4902**	**32.28**
012.run	405408	**4991**	**32.87**
013.run	406016	**4999**	**32.92**
014.run	400524	**4928**	**32.45**
Mean:		4961	32.67
S.D.		65.3	0.430

Exposure Day 10 6-11-03

6/11/2003	area counts	ppm	mg/L
.run	387051	**4753**	**31.30**
001.run	391981	**4817**	**31.72**
002.run	417150	**5144**	**33.88**
003.run	405088	**4987**	**32.84**
004.run	414223	**5106**	**33.62**
005.run	410671	**5060**	**33.32**
006.run	404164	**4975**	**32.76**
007.run	414112	**5105**	**33.62**
008.run	407968	**5025**	**33.09**
009.run	390794	**4801**	**31.62**
010.run	389188	**4781**	**31.48**
011.run	397799	**4892**	**32.22**
012.run	381019	**4674**	**30.78**
013.run	383535	**4707**	**31.00**
014.run	385049	**4727**	**31.13**
015.run	389333	**4782**	**31.49**
Mean:		4896	32.24
S.D.		159.7	1.052

Exposure Day 11 6-12-03

6/12/03 exposure	area counts	ppm	mg/L
.run	409682	**5047**	**33.24**
001.run	403131	**4962**	**32.68**
002.run	407320	**5016**	**33.03**
003.run	414456	**5109**	**33.64**
004.run	412202	**5080**	**33.45**
005.run	411341	**5068**	**33.38**
006.run	412566	**5084**	**33.48**
007.run	411948	**5076**	**33.43**
008.run	417518	**5149**	**33.91**
009.run	414394	**5108**	**33.64**
010.run	419362	**5173**	**34.06**
011.run	413685	**5099**	**33.58**
012.run	421161	**5196**	**34.22**
013.run	416328	**5133**	**33.80**
014.run	405684	**4995**	**32.89**
015.run	404292	**4977**	**32.77**
Mean:		5080	33.45
S.D.		67.7	0.446

Exposure Day 12 6-13-03

6/13/03 exposure	area counts	ppm	mg/L
.run	360622	**4409**	**29.04**
001.run	376763	**4619**	**30.42**
002.run	396802	**4880**	**32.13**
003.run	416102	**5130**	**33.79**
004.run	422885	**5219**	**34.37**
005.run	417235	**5145**	**33.88**
006.run	417849	**5153**	**33.93**
007.run	417566	**5149**	**33.91**
008.run	414576	**5111**	**33.65**
009.run	415540	**5123**	**33.74**
010.run	415234	**5119**	**33.71**
011.run	413338	**5094**	**33.55**
012.run	418510	**5162**	**33.99**
013.run	420935	**5193**	**34.20**
014.run	422000	**5207**	**34.29**
015.run	410245	**5054**	**33.28**
Mean:		5048	33.24
S.D.		225.6	1.485

Exposure Day 13 6-14-03

6/14/03 exposure 5000ppm bag	area counts	ppm	mg/L
check001.run	420026	**5181**	**34.12**
.run	404437	**4979**	**32.79**
001.run	425945	**5258**	**34.63**
002.run	400293	**4925**	**32.43**
003.run	411711	**5073**	**33.41**
004.run	404699	**4982**	**32.81**
005.run	413758	**5100**	**33.58**
006.run	398464	**4901**	**32.28**
007.run	400628	**4929**	**32.46**
008.run	401982	**4947**	**32.58**
009.run	405963	**4999**	**32.92**
010.run	398328	**4899**	**32.26**
011.run	394936	**4855**	**31.97**
012.run	407350	**5017**	**33.04**
013.run	401054	**4935**	**32.50**
014.run	396051	**4870**	**32.07**
015.run	399987	**4921**	**32.41**
Mean:		4987	32.84
S.D.		110.3	0.727

Exposure Day 14 6-15-03

6/15/03 exposure	area counts	ppm	mg/L
.run	408127	**5027**	**33.10**
001.run	403426	**4966**	**32.70**
002.run	408455	**5031**	**33.13**
003.run	416106	**5130**	**33.79**
004.run	406171	**5001**	**32.94**
005.run	409169	**5040**	**33.19**
006.run	413930	**5102**	**33.60**
007.run	407124	**5014**	**33.02**
008.run	405413	**4991**	**32.87**
009.run	399176	**4910**	**32.34**
010.run	401987	**4947**	**32.58**
011.run	406287	**5003**	**32.95**
012.run	409677	**5047**	**33.24**
013.run	401438	**4940**	**32.53**
Mean:		5011	33.00
S.D.		60.3	0.397

Exposure Day 15 6-16-03

6/16/03 exposure	area counts	ppm	mg/L
.run	421144	**5196**	**34.22**
001.run	441504	**5461**	**35.96**
002.run	436580	**5397**	**35.54**
003.run	425393	**5251**	**34.58**
004.run	437551	**5409**	**35.62**
005.run	425346	**5251**	**34.58**
006.run	435145	**5378**	**35.42**
007.run	442581	**5475**	**36.05**
008.run	432220	**5340**	**35.17**
009.run	436329	**5393**	**35.52**
010.run	432898	**5349**	**35.22**
011.run	434668	**5372**	**35.37**
012.run	436278	**5393**	**35.51**
013.run	433004	**5350**	**35.23**
014.run	434123	**5365**	**35.33**
015.run	435091	**5377**	**35.41**
016.run	436398	**5394**	**35.52**
017.run	435791	**5386**	**35.47**
018.run	436662	**5398**	**35.55**
019.run	433900	**5362**	**35.31**
Mean:		5365	35.33
S.D.		66.6	0.438

Single Exposure Day 1 9-29-03

9/29/03 exposure .run	area counts	ppm	mg/L
	242278	**4412**	**29.06**
001.run	249744	**4553**	**29.98**
002.run	272776	**4987**	**32.84**
003.run	274947	**5028**	**33.11**
004.run	274793	**5025**	**33.09**
005.run	275596	**5040**	**33.19**
006.run	277555	**5077**	**33.43**
007.run	274228	**5014**	**33.02**
008.run	277453	**5075**	**33.42**
009.run	275945	**5047**	**33.23**
010.run	273699	**5004**	**32.96**
011.run	279973	**5123**	**33.73**
012.run	274332	**5016**	**33.03**
013.run	278878	**5102**	**33.60**
014.run	278823	**5101**	**33.59**
015.run	278866	**5102**	**33.60**
016.run	276404	**5055**	**33.29**
017.run	275395	**5036**	**33.17**
Mean:		4989	32.85
S.D.		189.6	1.248

APPENDIX C – Parent and Radioactivity Data

Procedure for Determination of HMDS in Biological Matrices (Blood and Tissues)

Study 9829

Joseph M Tobin Date 6/12/03

Joe Tobin, B.S.
Study Director

Debra A. McNett Date June 12, 2003

Debra A. McNett, B.S.
Bioanalytical Supervisor

PROCEDURE FOR DETERMINATION OF HMDS IN BIOLOGICAL MATRICES (Blood and Tissues)

PURPOSE

To describe a method for extraction and quantification of Hexamethyldisiloxane (HMDS) in biological matrices.

EQUIPMENT

1. Chemicals
   a. Hexamethyldisiloxane (HMDS) — supplied by DCC
   b. ^{13}C-Hexamethyldisiloxane (HMDS) — supplied by DCC
   c. Tetrahydrofuran anhydrous 99.9% (THF) — supplied by Aldrich
   d. Magnesium sulfate ($MgSO_4$) — supplied by Fisher

2. Equipment

GC/MS HP Chemstation Software	HP 6890	Hewlett Packard
Column 30m x 0.25mm ID, 0.25μm film thickness	HP-5 MS	Hewlett Packard
Centrifuge Beckman GS-6R		IEC Contra-8R Centrifuge
Vortexer		VWR Multi-Tube Vortexer
Autosampler vials glass	2 mL crimp top, clear	Hewlett Packard
Limited volume	inserts 100uL glass	Alltech
Aluminum crimp caps	teflon-lined red/orange butyl rubber septa	Hewlett Packard
Extractant collection vials and caps	glass – PTFE lined	Alltech
Round bottom vial glass	1.7 mL crimp top, clear	Alltech
scissors	stainless steel surgical	

Note: equivalent equipment may be substituted for any of the above.

3. General

An analytical balance shall be used for gravimetric preparation of all standards and samples on a weight of solute per weight of solution basis. Volumetric addition of QC spike can be made if syringe test (5 replicate weights of 20 uL addition of QC spike solution into GC autosample vial. The average weight per uL will be used to calculate expected concentration of QC spikes.

PREPARATION OF REAGENTS

1. Internal Standard Stock Preparation

Accurately weigh and record to the nearest 0.1mg in a glass vial previously capped and tared, approximately 15.0 mg of M_4Q or ^{13}C-HMDS (IS). Add approximately 18 mL of THF, obtain final weight of solution and mix well. (Concentration approximately 900000 ng/g).

2. Internal Standard Working Solution

The internal standard working solution (ISTD) which is added to all working solvent standards and QC matrix samples consists of THF containing (IS). To prepare 100 mL of internal standard solution, weigh and record to the nearest 0.1 mg, approximately 6 mL of internal standard stock solution in a suitable glass vial. Add approximately 100 mL of THF, cap and vortex gently for 30 seconds. Obtain the final weight of the standard solution. (Concentration approximately 54000 ng/g).

3. Standard Preparation (STD)

3.1 STD STK

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg, approximately 25.0 mg of HMDS. Add approximately 10 mL of THF, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and THF. (Concentration approximately 2810000 ng/g).

3.2 STD STK 1

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.5mL of STD STK (above). Add approximately 10 mL of THF, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and THF. (Concentration approximately 140500 ng/g)

3.3 STD STK 2

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.25mL of STD STK 1 (above). Add approximately 10 mL of THF, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and THF. (Concentration approximately 3512 ng/g)

4. QC Stock Solution Preparation

4.1 QC STK

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg, approximately 15.0 mg of HMDS. Add approximately 10 mL of THF, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and THF. (Concentration approximately 1700000 ng/g).

4.2 QC STK 1

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.6mL of QC STK (above). Add approximately 10 mL of THF, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and THF. (Concentration approximately 102000 ng/g)

4.3 QC STK 2

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.10mL of QC STK (see section 4.1). Add approximately 10 mL of THF, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and THF. (Concentration approximately 17000 ng/g).

4.4 QC STK Livers

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg, approximately 100mg of HMDS. Add approximately 9 mL of THF, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and THF (12,500,000 ng/g)

NOTE:
Record all STD STK and QC STK preparation information on an appropriate form.
Reagent volumes and weights may be adjusted as long as exact concentrations are known.

STD CURVE PREPARATION

Place approximately 250 mg of $MgSO_4$ into round bottom glass vials. Prepare solvent standards with the appropriate standard stock solution and internal standard solution according to the following table. Obtain the weight of the aliquot of standard stock and the aliquot of internal standard solution placed in the vial containing $MgSO_4$ all to the nearest 0.1mg. Vortex each standard approximately 15 seconds. Dry (with $MgSO_4$) at least 1 hour. Centrifuge each standard at a setting of 2800 rpm for approximately 15 min. Place an aliquot of each standard in a limited volume insert in an autosampler vial and analyze by GC/MS.

TABLE 1: STD Curve

Standard ID	Volume of STD STK (mL)	STD STK used	Volume of Internal standard solution (mL)	Total Volume (mL)	Approximate amount of IS added (ng)	Approximate amount HMDS added (ng)
Blank	0	none	0.5	1.00	27000	0.0
50	0.015	STD STK 2	0.5	1.00	27000	52.7
100	0.030	STD STK 2	0.5	1.00	27000	105.4
200	0.060	STD STK 2	0.5	1.00	27000	210.7
500	0.150	STD STK 2	0.5	1.00	27000	526.8
1000	0.290	STD STK 2	0.5	1.00	27000	1018.5
1500	0.430	STD STK 2	0.5	1.00	27000	1510.2
2000	0.015	STD STK 1	0.5	1.00	27000	2107.5
4000	0.030	STD STK 1	0.5	1.00	27000	4215.0
8000	0.060	STD STK 1	0.5	1.00	27000	8430.0
12000	0.090	STD STK 1	0.5	1.00	27000	12645.0
16000	0.120	STD STK 1	0.5	1.00	27000	16860.0
20000	0.145	STD STK 1	0.5	1.00	27000	20372.5
25000	0.180	STD STK 1	0.5	1.00	27000	25290.0
45000	0.300	STD STK 1	0.5	1.00	27000	42150.0
70000	0.500	STD STK 1	0.5	1.00	27000	70250.0
100000	0.035	STD STK	0.5	1.00	27000	98350.0
150000	0.050	STD STK	0.5	1.00	27000	140500.0
200000	0.070	STD STK	0.5	1.00	27000	196700.0
300000	0.110	STD STK	0.5	1.00	27000	309100.0

STD (ng) = Concentration STDSTK or STD STK1 or STD STK 2) (ng/g) X Wt. of STD (g)

Standard stock solutions and working standard solutions are stable at (5 ± 4°C) for up to 9 days.

QC SAMPLE PREPARATION

Prepare each matrix spike in duplicate according to the table below. Place approximately 250mg of matrix (blood) into the appropriate vials and spike with appropriate QC stock solution as shown below. Volumes are given for comparison, but obtain weights of all aliquots for calculation purposes (to the nearest 0.1mg).

Table 2: QC Matrix Samples (blood)

Standard ID	Volume of STD STK (mL)	STD STK used	Volume of Internal standard solution (mL) (1st extract)	Total Volume[a] (mL)	Approximate amount of IS added (ng)	Approximate amount HMDS added (ng)
QC-0	0.000	none	0.5	1.00	27000	0
QC-1	0.020	QC STK 2	0.5	1.00	27000	340
QC-2	0.025	QC STK 1	0.5	1.00	27000	2550
QC-3	0.007	QC STK	0.5	1.00	27000	11900
QC-4	0.015	QC STK	0.5	1.00	27000	25500

[a] Total volume is based on 1 extraction at approximately 0.5 mL of internal standard solution (weight obtained) and an additional extraction at approximately 0.5 mL of THF.

For fat QC samples, prepare each level in duplicate. Place fat sample (approximately 250mg to 1g) into an appropriate vial and spike with the appropriate QC stock solution as shown below. For kidney, testes and lung QC samples, prepare each level in duplicate. Place a kidney, a teste or one lobe of a lung into an appropriate vial and spike in the matrix with appropriate QC stock solution as shown below. Syringe test: Using QC STK and syringe make 5 replicate weights of 20 uL additions of QC spike solution into a autosample vial and record weight. The average weight per uL will be used to determine the expected concentration of the QC samples.

Table 3: QC Matrix Samples (fat, kidney, testes, brain and lung)

Standard ID	Volume of STD STK (mL)	STD STK used	Volume of Internal standard solution (mL) (1st extract)	Total Volume[a] (mL)	Approximate amount of IS added (ng)	Approximate amount HMDS added (ng)
QC-0	0.000	none	0.5	6.00	27000	0
QC-1	0.020	QC STK 2	0.5	6.00	27000	340
QC-2	0.020	QC STK 1	0.5	6.00	27000	2040
QC-3	0.005	QC STK	0.5	6.00	27000	8500
QC-4	0.010	QC STK	0.5	6.00	27000	17000

[a] Total volume is based on 1 extraction at approximately 0.5 mL of internal standard solution (weight obtained) followed by addition of approximately 5.5 mL of THF.

For Liver QC samples, prepare each level in duplicate. Place one half liver into an appropriate vial and spike in the liver with appropriate QC stock solution as shown below. Syringe test: Using QC STK Liver and syringe, make 5 replicate weights of 20 uL additions of QC spike solution into a autosample vial and record weight. The average weight per uL will be used to determine the expected concentration of the QC samples.

Table 4: QC Matrix Samples (liver)

Standard ID	Volume of STD STK (mL)	STD STK used	Volume of Internal standard solution added (mL)	Total Volume[a] (mL)	Approximate amount of IS added (ng)	Approximate amount HMDS added (ng)
QC-0	0.000	none	0.5	40.5	27000	0.00
QC-1	0.005	QC STK Liver	0.5	40.5	27000	62500
QC-2	0.015	QC STK Liver	0.5	40.5	27000	187500
QC-3	0.025	QC STK Liver	0.5	40.5	27000	312500

[a] Total volume is based on addition of approximately 0.5 mL of internal standard solution (weight obtained) followed by addition of approximately 40 mL THF.

QC samples are then extracted with THF according to the Sample Preparation Section below starting with step 1.2, (do not add blood in step 1.3), 2.3, 3.3, or 4.3 depending on the matrix used.

SAMPLE PREPARATION

1. Blood Extraction

   1.1. Add ~5 glass beads to extraction vial, use septa cap for vial.

   1.2. Add ~0.5 mL of internal standard solution and obtain weight.

   1.3. Add approximately 150-250 mg of Blood; obtain weight, and vortex at least 5 minutes.

   1.4. Centrifuge at least 5 minutes at 2800 rpm and transfer the supernatant to a new pre-weighed glass vial.

   1.5. Add 0.5mL of THF to the blood vial for a second extraction and vortex at least 5 minutes.

   1.6. Centrifuge at least 5 minutes at 2800 rpm and transfer the supernatant to the same glass vial containing the first extract. Obtain weight of combined extracts. (note: extractant weight only needed if extractant will be used for Radiochemical analysis.)

   1.7. Add approximately 250 mg of $MgSO_4$ to glass round bottom vials. Transfer ~600uL of each of the above extracts to the glass round bottom vials, cap and vortex for approximately 15 seconds, and allow to dry at least 1 hour.

   1.8. Centrifuge the samples for at least 15 minutes at 2800 rpm.

   1.9. Transfer an aliquot of the supernatant to a low volume insert in a GC autosampler vial.

2. Fat, Kidney, Testes, Brain and Lung

   2.1. Obtain vial containing (weight previously obtained) tissue sample. (If frozen allow to thaw on ice.)

   2.2. Remove from ice, wipe water from outside of vial and obtain tare weight of vial (or tare balance) containing sample.

   2.3. Remove cap, add 0.5mL of internal standard solution, obtain weight, and add additional 5.5 mL of THF.

   2.4. With scissors, cut tissue into small pieces to improve surface area contact with THF.

   2.5. Vortex at least 5 minutes.

2.6. Centrifuge at least 5 minutes at 2800 rpm and transfer the supernatant to the same glass vial containing the first extract. Obtain weight of combined extracts. (note: extractant weight only needed if extractant will be used for Radiochemical analysis.)

2.7. Add approximately 250 mg of $MgSO_4$ to glass round bottom vials. Transfer ~600uL of each of the above extracts to the glass round bottom vials, cap and vortex for approximately 15 seconds, and allow to dry at least 1 hour.

2.8. Centrifuge the samples for at least 15 minutes at 2800 rpm.

2.9. Transfer an aliquot of the supernatant to a low volume insert in a GC autosampler vial.

3. Liver Extraction

3.1. Obtain jar (weight previously obtained) containing liver sample. (If frozen allow to thaw on ice.)

3.2. Remove from ice, wipe water from outside of jar and obtain tare weight of vial (or tare balance) containing the sample.

3.3. Remove cap, add 0.5mL of internal standard solution and obtain weight. Add an additional 40.0 mL of THF.

3.4. With scissors, cut liver into small pieces to improve surface area contact with THF.

3.5. Vortex at least 5 minutes.

3.6. Centrifuge at least 5 minutes at 2800 rpm and transfer the supernatant to a new pre-weighed 4 oz glass jar. Obtain weight of the extract. (note: extractant weight only needed if extractant will be used for Radiochemical analysis.)

3.7. Add approximately 250 mg of $MgSO_4$ to glass round bottom vials. Transfer an aliquot of each of the above extracts (approximately 600uL) to the glass round bottom vials, cap and vortex for approximately 15 seconds, and allow to dry at least 1 hour.

3.8. Centrifuge the samples for at least 15 minutes at 2800 rpm.

3.9. Transfer an aliquot of the supernatant to a low volume insert in a GC autosampler vial.

Note: Once samples are in extraction solvent, liver, fat and brain extraction samples are stable up to 9 days at a temperature no warmer than 5±4 degrees C. Blood, lung, kidney and testes extractions samples are stable up to 9 days at –20 ±4 degrees C.

ANALYSIS

Samples shall be analyzed by GC/MS using the instrument parameters shown in Table 5.

Injection and oven ramp parameters may be edited as long as the same parameters are used for solvent standards, QC samples and samples for a given analysis.

Table 5. Analysis Parameters

Instrument:	Hewlett Packard 6890 Gas Chromatograph/Mass Selective Detector		
Column:	Hewlett Packard HP-5MS 30m x 0.25mm ID with 0.25um film thickness		
Carrier Gas:	Helium, initial pressure 7.5 psi, 1.0 mL/min, constant flow on		
Injection:	temperature 250°C, splitless, 1uL injection		
Oven Ramp:	Initial 50°C for 2.5 min, ramp to 230°C at 40°C/min, hold for 1 min, total run time 8.0 min.		
Detection:	MSD transfer line temperature 280°C		
	Quantitation ions:	HMDS:	147 m/z at 100msec
		13C-HMDS	152 m/z at 100msec

Single injection analysis of each sample is sufficient.

Sample Analysis Order (Example)
Analyze each matrix in separate analysis runs. Separate analysis runs may occur on the same day.

Solvent Blank
Solvent Internal Standard Blank (3 injections)
Solvent Calibration Standards, (Low to High)
Solvent Blank
QC Samples (Low to High)
Solvent Blank
Solvent Standard
Sample Blank
10 Samples or Less
Solvent Standard
Sample Blank

Repeat this Solvent standard and Sample analysis pattern until all samples are analyzed.

DATA ANALYSIS

This section describes the calculations for the calibration of the GC/MS and the method to determine the amount of HMDS per gram of blood, liver, lung, fat, kidney, brain and testes.

All calculations for routine sample analysis shall be performed using a Microsoft Excel spreadsheet (a spreadsheet which has been prepared for a specific application and has been confirmed by an independent review to perform calculations as defined; subsequent uses of the spreadsheet require 100% check of all entered data). Non-routine calculations shall be prepared and reviewed as directed by the Study Director (or designee).

1. Instrument Calibration Calculations

   Calibration of the mass spectrometer is performed using HMDS concentrations expressed in terms of ng HMDS. The nominal concentrations of calibration standards are shown in Table 1. The standard curve may be split into up to 4 ranges depending on the range of the instrument as long as at least 4 standards make up a range.

   HMDS Calibration Equation

   Calculate a linear equation, using a suitable linear regression program, for HMDS where x = concentration (ng HMDS) and y = peak area response ratio for the calibration standards from the GC/MS analysis. Enter the resulting slope (m) and y-intercept (b) from each equation into the spreadsheet.

   $y = mx + b$, where y = peak area response ratio and x = ng HMDS

2. Calculation of HMDS Concentrations in Samples (ng HMDS)

   The concentration of HMDS in a sample extract is calculated once the slope (m) and y-intercept (b) have been entered into the spreadsheet. The concentration (ng HMDS) of HMDS in a sample extract is calculated by substitution of the peak area response ratio for y into the linear equation generated from calibration standards and solving for x, $(x = (y-b)/m)$.

3. Calculation of HMDS Concentrations in Samples (µg HMDS/g matrix)

   Calculation of HMDS concentration (µg/g) in sample matrix is as follows:

   HMDS (µg/g) = HMDS (ng) / Sample matrix weight (g) x 1µg/1000ng

   Note: An assumption is made that the amount of internal standard added (~0.5 mL) is the same for all samples and standards. If when obtaining the weights of these additions, it is found that the weights vary significantly (%CV > 5%), or at the discretion of the bioanalytical supervisor, then all calculations will have to be adjusted to correct for the differing amounts of internal standard added. For example, the calibration curve would be generated with x = ng HMDS/ng IS. Each sample would be calculated according to the calibration curve generated by solving for x (ng HMDS/ng IS). The amount of HMDS (ng) in each sample is then calculated by multiplying the ratio found (ng HMDS/ng IS) by the ng IS added. The subsequent calculations for determining ug HMDS/g sample would be the same as described above.

DATA ACCEPTANCE

1. Calibration Acceptance Criteria

   Agreement between the analyzed and prepared concentrations of HMDS in the calibration standards must be achieved to prove conformance to the linear calibration model. The percent relative error, calculated by the qualified spreadsheet, shall be used to prove conformance and is calculated by subtracting the analyzed concentration from the prepared concentration, and then dividing by the prepared concentration and multiplying by 100. The percent relative error shall be within 15% for every calibration standard analyzed for the calibration to be acceptable. Calibrations that do not meet these requirements shall be brought to the attention of the Bioanaltical Supervisor (or designee). Exceptions to this calibration acceptance criteria shall be made if all samples are bracketed by calibration standards that did meet the calibration acceptance criteria. The solvent standards that are run intermittently throughout the run are to be within 15% for the run to be accepted. Any samples run before a standard meeting this acceptance criteria will be accepted. If any standards do not meet this acceptance criteria, any samples run after the standard will be evaluated by the bioanalytical supervisor if they will be accepted.

REPORTING AND DATA COMPLETION

The chemistry technician shall be responsible for submission of a completed data packet to the Study Director (or designate). This data packet shall include, as a minimum:

1. Hard copies of GC/MS data (including instrument parameters and sequence)
2. The calibration curve and the data from which it was generated
3. Data reduction spreadsheet

The chemistry technician may also be responsible for completion of the notebook:

1. Calibration Standard Form attached in notebook and completed
2. QC Sample Preparation Form attached in notebook and completed
3. One page describing which samples were analyzed and any other comments on sample workup and analysis

QUALITY CONTROL

The chemistry technician shall check the data packet for accuracy and completeness prior to forwarding to the Study Director (or designate). The Study Director (or designate) shall provide a one-over-one check for accuracy and completeness and ensure that all GLP record keeping practices were correctly performed.

Procedure for Determination of HMDS in Expired Volatiles (Charcoal Tubes)

Study 9829

Joseph M Tobin Date 6/12/03

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PROCEDURE FOR DETERMINATION OF HMDS EXPIRED VOLATILES (CHARCOAL TUBES)

PURPOSE

To describe a method for extraction and quantification of Hexamethyldisiloxane (HMDS) in expired volatiles that have been trapped on charcoal tubes.

EQUIPMENT

1. Chemicals
   a. Hexamethyldisiloxane (HMDS) — supplied by DCC
   b. ^{13}C-Hexamethyldisiloxane (HMDS) — supplied by DCC
   c. Hexanes 99.9% — supplied by Fisher
   d. Magnesium sulfate ($MgSO_4$) — supplied by Fisher

2. Equipment

GC/MS HP Chemstation Software	HP 6890	Hewlett Packard
Column 30m x 0.25mm ID, 0.25µm film thickness	HP-5 MS	Hewlett Packard
Merlin Microseal Microseal-H septum	Microseal-221 nut	Merlin Instrument Company
Centrifuge Beckman GS-6R		IEC Contra-8R Centrifuge
Vortexer		VWR Multi-Tube Vortexer
Autosampler vials	2 mL crimp top, clear glass	Hewlett Packard
Limited volume	inserts 100µL glass	Alltech
Aluminum crimp caps	teflon-lined red/orange butyl rubber septa	Hewlett Packard
Desorption vials	20 mL glass vials and caps	Fisher
Round bottom vial	1.7 mL crimp top, clear glass	Alltech
Small file or glass scoring tool		Fisher
Tweezers		Fisher

Note: equivalent equipment may be substituted for any of the above.

3. General

An analytical balance shall be used for gravimetric preparation of all standards and samples on a weight of solute per weight of solution basis.

PREPARATION OF REAGENTS

1.1 Internal Standard Stock A Preparation

Accurately weigh and record to the nearest 0.1mg in a glass vial previously capped and tared, approximately 10.0 mg of ^{13}C-Hexamethyldisiloxane (HMDS). Add approximately 2.5 mL of hexane, cap and vortex gently for 30 seconds. Obtain the final weight of the standard solution. (Concentration approximately 6000000 ng/g).

2.1 Internal Standard Working Solution (hexane/ISTD)

The internal standard working solution (hexane/ISTD) which is used as the dilution/extraction solvent for all working solvent standards, QC matrix samples and study samples, consists of hexane containing ^{13}C-Hexamethyldisiloxane (HMDS) (IS). To prepare 4L of internal standard working solution, remove 1.6 mL of hexane from a 4L bottle of hexane and using a 10mL pipette, transfer 1.6 mL of Internal Standard Stock A(above) into the 4L bottle of hexane. Mix thoroughly and clearly identify the bottle with the new solution. (Concentration approximately 2400 ng/g).

3. Standard Preparation (STD)

3.1 STD STK A

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg, approximately 50.0 mg of HMDS. Add approximately 12.5 mL of hexane/ISTD, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane/ISTD. (Concentration approximately 6000000 ng/g).

3.2 STD STK B

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.05mL of STD STK A (above). Add approximately 12.5 mL of hexane/ISTD, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane/ISTD. (Concentration approximately 24000 ng/g)

3.3 STD STK 1000

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.63mL of STD STK B (above). Add approximately 10 mL of hexane/ISTD, cap and

vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane/ISTD. (Concentration approximately 1512 ng/g)

3.4 STD STK 100

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 1.0mL of STD STK 1000 (above). Add approximately 10 mL of hexane/ISTD, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane/ISTD. (Concentration approximately 150 ng/g)

4. QC Stock Solution Preparation

4.1 QC STK 200

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg, approximately 150.0 mg of HMDS. Add approximately 0.75mL of Hexane, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane. (Concentration approximately 300mg/g).

4.2 QC STK 50

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.25mL of QC STK 200 (above). Add approximately 1 mL of Hexane, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane. (Concentration approximately 75mg/g)

4.3 QC STK 5

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.1mL of QC STK 50 (above). Add approximately 1 mL of Hexane, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane. (Concentration approximately 7.5mg/g).

4.4 QC STK 0.2

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.04mL of QC STK 5 (above). Add approximately 1 mL of Hexane, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane. (Concentration approximately 0.3mg/g).

NOTE:
Record all STD STK and QC STK preparation information on an appropriate form.
Reagent volumes and weights may be scaled up or down proportionally.

vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane/ISTD. (Concentration approximately 1512 ng/g)

3.4 STD STK 100

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 1.0mL of STD STK 1000 (above). Add approximately 10 mL of hexane/ISTD, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane/ISTD. (Concentration approximately 150 ng/g)

4. QC Stock Solution Preparation

4.1 QC STK 200

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg, approximately 150.0 mg of HMDS. Add approximately 0.75mL of Hexane, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane. (Concentration approximately 300mg/g).

4.2 QC STK 50

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.25mL of QC STK 200 (above). Add approximately 1 mL of Hexane, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane. (Concentration approximately 75mg/g)

4.3 QC STK 5

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.1mL of QC STK 50 (above). Add approximately 1 mL of Hexane, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane. (Concentration approximately 7.5mg/g).

4.4 QC STK 0.2

In a suitable glass vial, previously capped and tared, weigh and record to the nearest 0.1 mg approximately 0.04mL of QC STK 5 (above). Add approximately 1 mL of Hexane, cap and vortex gently for 30 seconds at motor speed 2. Obtain the final weight of standard and hexane. (Concentration approximately 0.3mg/g).

NOTE:
Record all STD STK and QC STK preparation information on an appropriate form.
Reagent volumes and weights may be scaled up or down proportionally.

STD CURVE PREPARATION

Place approximately 250 mg of $MgSO_4$ into round bottom glass vials. Prepare solvent standards with the appropriate standard stock solution and hexane/ISTD solution according to the following table. Obtain the weight of the aliquot of standard stock and the final solution weight placed in the vial containing $MgSO_4$ all to the nearest 0.1mg. Vortex each standard approximately 15 seconds. Dry (with $MgSO_4$) at least 1 hour. Centrifuge each standard at a setting of 2800 rpm for approximately 15 min. Place an aliquot of each standard in a limited volume insert in an autosampler vial and analyze by GC-MS.

TABLE 1: Solvent Standards

Standard ID	Volume of STD STK (µL)	STD used	Volume of STK hexane/ISTD (µL)	Total Volume (mL)	Approximate Concentration of HMDS added (ng/g)
Blank	0	none	1000	1	0
20	200	STD STK 100	800	1	20
50	500	STD STK 100	500	1	50
75	750	STD STK 100	250	1	75
100	1000	STD STK 100	0	1	100
200	200	STD STK 1000	800	1	200
300	300	STD STK 1000	700	1	700
400	400	STD STK 1000	600	1	400
600	600	STD STK 1000	400	1	600
800	800	STD STK 1000	200	1	800
1000	1000	STD STK 1000	0	1	1000
2000	126	STD STK B	874	1	2016
4000	252	STD STK B	748	1	4032
6000	375	STD STK B	625	1	6000
8000	500	STD STK B	500	1	8000
10000	630	STD STK B	370	1	10080
12000	750	STD STK B	250	1	12000
Stock B	1000	STD STK B	0	1	16000
120000	30	STD STK A	970	1	120000
200000	50	STD STK A	950	1	200000
400000	100	STD STK A	900	1	400000

STD (ng/g) = Concentration STD STK used (ng/g) X Wt. of STD (g) / Total ~ weight (g)

QC SAMPLE PREPARATION

Prepare each matrix spike in duplicate according to the table below. Score the end of a blank charcoal tube and break the tip and remove. Fill a syringe to the mark indicated in the table below and weigh the syringe full. Spike the blank charcoal tube by placing the tip of the syringe into the level of charcoal. Weigh the empty syringe and by difference determine the weight of the spike.

Table 2: QC Charcoal Tube Samples

QC Sample ID	Volume of QC STK (uL)	QC STK used	Volume of hexane/ISTD for extraction (mL)	Total Volume (mL)	Approximate Concentration of HMDS added (ng/g)
0ug	0	none	15	15	0
2ug	10	QC STK 0.3	15	15.01	200
50ug	10	QC STK 7.5	15	15.01	5000
500ug	10	QC STK 75	15	15.01	50000
2000ug	10	QC STK 300	15	15.01	200000

QC charcoal tube samples are then extracted with hexane/ISTD according to the Sample Preparation Section below starting with step 1.b.

SAMPLE PREPARATION

1. Charcoal Tube Extraction

   a. Processing of the charcoal tubes should be done in the walk-in refrigerator using chilled hexane/ISTD*. (*Due to exothermic reaction caused by the addition of the charcoal to the hexane)
   b. Record information on the appropriate form.
   c. Score the end of the charcoal tube containing the cotton plug with a small file or glass scoring tool. Score it back from the end far enough to allow easy access to the cotton plug with tweezers.
   d. Break off the end of the charcoal tube.
   e. Crack the tube and deliver entire contents to a 20 ml scintillation vial containing ~15 ml of pre-weighed appropriate solvent (e.g. hexane/ISTD). Record the solvent weight.
   f. Wrap the caps of the vials with Teflon tape to prevent evaporation of solvent.
   g. Allow solvent to desorb analytes from charcoal for at least overnight.

   Radioactivity Analysis

   1) Label caps of LSC vials.
   2) Add approximately 6 ml of the scintillation cocktail to each of two 7 ml scintillation vials. If 20 ml scintillation vials are used, add approximately 15 ml of scintillation cocktail.
   3) Remove two 100 - 500 µl aliquots of solvent from the vial containing the charcoal and transfer them to the two scintillation vials.
   4) Record the weights of the aliquots.
   5) Mix gently, and place vials in a scintillation counter tray for radioactivity analysis.

   GC/MS Analysis

   1) Place approximately 250mg of $MgSO_4$ in round bottom vials.
   2) Transfer approximately 600µL aliquots of the solvent above each charcoal sample to the vial containing $MgSO_4$ and allow drying for at least 1 hour.
   3) Centrifuge each of the above dried samples at a setting of 2800 rpm for approximately 15 min.

4) Place an aliquot of each standard in a limited volume insert in an autosampler vial and analyze by GC-MS.

Note: Once samples are in extraction solvent, samples are stable up to 5 days at 5±4°C.

ANALYSIS

Samples shall be analyzed by GC/MS using the instrument parameters shown in Table 3.

Injection and oven ramp parameters may be edited as long as the same parameters are used for solvent standards, QC samples and samples for a given analysis.

Table 3. Analysis Parameters

Instrument:	Hewlett Packard 6890 Gas Chromatograph/Mass Selective Detector		
Column:	Hewlett Packard HP-5MS 30m x 0.25mm ID with 0.25um film thickness		
Carrier Gas:	Helium, initial pressure 10.5 psi, 1.0 mL/min, constant flow on		
Injection:	temperature 250°C, splitless, purge time 0.20min, 2µL injection		
Oven Ramp:	Initial 50°C for 3.0 min, ramp to 210°C at 17°C/min, ramp to 250°C at 30°C/min hold for 1 min, total run time 11.80 min.		
Detection:	MSD transfer line temperature 280°C		
	Quantitation ions:	HMDS:	147 m/z at 100msec
		13C-HMDS:	152 m/z at 100msec

Single injection analysis of each sample is sufficient.

Sample Analysis Order (Example)
Analyze each matrix in separate analysis runs. Separate analysis runs may occur on the same day.

Solvent Blank
Solvent Internal Standard Blank (3 injections)
Solvent Calibration Standards, (Low to High)
Solvent Blank
QC Samples (Low to High)
Solvent Blank
Solvent Standard
Sample Blank
10 Samples or Less
Solvent Standard
Sample Blank

Repeat this Solvent standard and Sample analysis pattern until all samples are analyzed.

DATA ANALYSIS

This section describes the calculations for the calibration of the GC/MS and the method to determine the amount of HMDS in each charcoal tube.

All calculations for routine sample analysis shall be performed using a Microsoft Excel spreadsheet (a spreadsheet which has been prepared for a specific application and has been confirmed by an independent review to perform calculations as defined; subsequent uses of the spreadsheet require 100% check of all entered data). Non-routine calculations shall be prepared and reviewed as directed by the Study Director (or designee).

1. Instrument Calibration Calculations

   Calibration of the mass spectrometer is performed using HMDS concentrations expressed in terms of ng HMDS/g hexane. The nominal concentrations of calibration standards are shown in Table 1. The standard curve may be split into up to 3 ranges depending on the range of the instrument as long as at least 4 standards make up a range.

   HMDS Calibration Equation

   Calculate a linear equation, using a suitable linear regression program, for HMDS where x = concentration (ng HMDS/g) and y = peak area response ratio for the calibration standards from the GC/MS analysis. Enter the resulting slope (m) and y-intercept (b) from each equation into the spreadsheet.

   $y = mx + b$, where y = peak area response ratio and x = ng HMDS/g

2. Calculation of HMDS Concentrations in Samples (µg HMDS)

   The concentration of HMDS in a sample extract is calculated once the slope (m) and y-intercept (b) have been entered into the spreadsheet. The concentration (ng HMDS/g hexane) of HMDS in a sample extract is calculated by substitution of the peak area response ratio for y into the linear equation generated from calibration standards and solving for x, $(x = (y-b)/m)$.

3. Calculation of HMDS Concentrations in Samples (µg HMDS)
   Calculation of HMDS concentration (µg) in sample matrix is as follows:

   HMDS (µg) = HMDS(ng)/g hexane * g hexane/ISTD used for extraction x 1µg/1000ng

DATA ACCEPTANCE

1. Calibration Acceptance Criteria

Agreement between the analyzed and prepared concentrations of HMDS in the calibration standards must be achieved to prove conformance to the linear calibration model. The percent relative error, calculated by the qualified spreadsheet, shall be used to prove conformance and is calculated by subtracting the analyzed concentration from the prepared concentration, and then dividing by the prepared concentration and multiplying by 100. The percent relative error shall be within 15% for every calibration standard analyzed for the calibration to be acceptable. Calibrations that do not meet these requirements shall be brought to the attention of the Bioanalytical Supervisor (or designee). Exceptions to this calibration acceptance criteria shall be made if all samples are bracketed by calibration standards that did meet the calibration acceptance criteria. The solvent standards that are run intermittently throughout the run are to be within 15% for the run to be accepted. Any samples run before a standard meeting this acceptance criteria will be accepted. If any standards do not meet this acceptance criteria, any samples run after the standard will be evaluated by the bioanalytical supervisor if they will be accepted.

REPORTING AND DATA COMPLETION

The chemistry technician shall be responsible for submission of a completed data packet to the Study Director (or designate). This data packet shall include, as a minimum:

1. Hard copies of GC/MS data (including instrument parameters and sequence)
2. The calibration curve and the data from which it was generated
3. Data reduction spreadsheet

The chemistry technician shall also be responsible for completion of the notebook:

1. Calibration Standard Form attached in notebook and completed
2. QC Sample Preparation Form attached in notebook and completed
3. One page describing which samples were analyzed and any other comments on sample workup and analysis

QUALITY CONTROL

The chemistry technician shall check the data packet for accuracy and completeness prior to forwarding to the Study Director (or designate). The Study Director (or designate) shall provide a one-over-one check for accuracy and completeness and ensure that all GLP record keeping practices were correctly performed.

Blood Results Repeat Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0619	168	NA			BLQ		
D0625	-3	19.20	20.93	2.37	10.40	11.78	0.52
D0626	-3	17.24			12.71		
D0627	-3	19.40			11.55		
D0628	-3	27.89			12.46		
D0629	0	98.52	98.35	3.70	11.90	12.44	0.51
D0630	0	102.74			12.11		
D0631	0	104.28			13.97		
D0632	0	87.86			11.79		
D0633	0.17	111.37	97.64	8.91	5.04	5.89	0.31
D0634	0.17	78.37			6.35		
D0635	0.17	114.14			5.84		
D0636	0.17	86.67			6.32		
D0637	0.5	101.29	101.34	4.56	3.12	2.87	0.16
D0638	0.5	111.41			2.57		
D0639	0.5	89.35			2.93		
D0640	0.5	103.30			2.40		
D0641	1	108.70	93.55	7.55	2.32	2.06	0.21
D0642	1	102.37			1.46		
D0643	1	74.85			2.33		
D0644	1	88.30			2.12		
D0645	2	123.76	109.68	8.33	1.24	1.28	0.03
D0646	2	89.21			1.22		
D0647	2	122.75			1.30		
D0648	2	102.99			1.36		
D0649	12	24.80	22.69	1.04	0.42	0.46	0.02
D0650	12	23.83			0.51		
D0651	12	20.08			0.50		
D0652	12	22.06			0.43		
D0653	24	7.69	8.91	0.49	0.42	0.40	0.07
D0654	24	8.65			0.28		
D0655	24	9.96			0.58		
D0656	24	9.33			0.33		
D0657	72	1.87	2.02	0.06	BLQ	N/AP	N/AP
D0658	72	2.15			BLQ		
D0659	72	2.05			BLQ		
D0660	72	2.00			BLQ		
D0661	120	0.94	1.15	0.09	BLQ	N/AP	N/AP
D0662	120	1.24			BLQ		
D0663	120	1.35			BLQ		
D0664	120	1.06			BLQ		
D0665	168	1.12	1.03	0.04	BLQ	N/AP	N/AP
D0666	168	1.14			BLQ		
D0667	168	0.96			BLQ		
D0668	168	0.95			BLQ		
D0669	168	0.97			BLQ		

Blood Results Single Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0952	168	NA			BLQ		
D0958	-3	17.24	12.84	1.57	11.81	11.07	0.32
D0959	-3	12.35			11.23		
D0960	-3	11.95			10.28		
D0961	-3	9.83			10.97		
D0962	0	31.28	28.62	1.29	11.74	11.58	0.44
D0963	0	28.63			11.19		
D0964	0	29.45			12.72		
D0965	0	25.12			10.67		
D0966	0.17	22.37	22.64	0.69	5.76	6.34	0.25
D0967	0.17	23.68			6.32		
D0968	0.17	23.71			6.96		
D0969	0.17	20.80			6.33		
D0970	0.5	25.23	30.24	2.87	2.89	2.75	0.12
D0971	0.5	29.37			2.52		
D0972	0.5	38.46			2.84		
D0973	0.5	27.91			3.12		
D0974	1	20.39	25.38	2.63	2.62	2.28	0.15
D0975	1	23.20			2.17		
D0976	1	25.22			2.42		
D0977	1	32.70			1.93		
D0978	2	33.84	37.00	4.87	1.46	1.44	0.05
D0979	2	25.15			1.58		
D0980	2	47.82			1.34		
D0981	2	41.17			1.38		
D0982	12	17.25	19.25	1.57	0.34	0.45	0.05
D0983	12	16.48			0.39		
D0984	12	19.80			0.53		
D0985	12	23.46			0.55		
D0986	24	8.59	9.07	0.29	0.49	0.39	0.04
D0987	24	9.63			0.37		
D0988	24	8.56			0.29		
D0989	24	9.49			0.39		
D0990	72	2.15	1.97	0.09	BLQ	N/AP	N/AP
D0991	72	2.05			BLQ		
D0992	72	1.95			BLQ		
D0993	72	1.73			BLQ		
D0994	120	1.05	0.92	0.08	BLQ	N/AP	N/AP
D0995	120	0.72			BLQ		
D0996	120	0.83			BLQ		
D0997	120	1.06			BLQ		
D0998	168	1.05	0.99	0.14	BLQ	N/AP	N/AP
D0999	168	1.04			BLQ		
D1000	168	1.45			BLQ		
D1001	168	0.71			BLQ		
D1002	168	0.68			BLQ		

Brain Results Repeat Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0619	168	NA			BLQ		
D0629	0	214.59	206.91	2.61	163.61	150.85	4.41
D0630	0	203.63			146.99		
D0631	0	203.66			143.58		
D0632	0	205.77			149.19		
D0645	2	120.12	107.24	8.11	11.17	11.49	0.48
D0646	2	88.22			12.26		
D0647	2	121.33			10.26		
D0648	2	99.30			12.27		
D0649	12	23.52	21.04	1.10	1.69	1.58	0.08
D0650	12	22.15			1.51		
D0651	12	18.63			1.73		
D0652	12	19.88			1.40		
D0653	24	6.75	7.76	0.61	0.97	1.01	0.05
D0654	24	6.74			0.93		
D0655	24	8.40			1.15		
D0656	24	9.17			0.99		
D0657	72	1.85	2.16	0.24	0.15	0.20	0.02
D0658	72	1.75			0.16		
D0659	72	2.80			0.24		
D0660	72	2.26			0.23		
D0661	120	1.14	1.02	0.15	0.07	0.06	0.00
D0662	120	1.14			0.06		
D0663	120	0.57			0.07		
D0664	120	1.22			0.07		
D0665	168	0.88	1.06	0.14	0.03	0.04	0.01
D0666	168	0.86			0.07		
D0667	168	1.59			0.05		
D0668	168	1.14			0.03		
D0669	168	0.83			0.02		

Brain Results Single Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0952	168	NA			BLQ		
D0962	0	158.52	161.62	1.96	130.67	129.57	3.25
D0963	0	167.35			138.34		
D0964	0	160.56			124.74		
D0965	0	160.05			124.53		
D0978	2	69.28	59.69	3.46	10.79	10.98	1.05
D0979	2	54.57			13.14		
D0980	2	60.21			11.78		
D0981	2	54.68			8.18		
D0982	12	26.09	26.59	1.17	1.31	1.57	0.12
D0983	12	24.98			1.49		
D0984	12	25.26			1.59		
D0985	12	30.01			1.88		
D0986	24	11.00	10.38	0.29	0.80	0.84	0.05
D0987	24	9.72			0.89		
D0988	24	10.11			0.72		
D0989	24	10.68			0.95		
D0990	72	1.61	1.61	0.09	0.18	0.16	0.01
D0991	72	1.85			0.18		
D0992	72	1.39			0.12		
D0993	72	1.60			0.17		
D0994	120	1.11	0.60	0.19	0.05	0.05	0.00
D0995	120	0.21			0.05		
D0996	120	0.45			0.05		
D0997	120	0.62			0.05		
D0998	168	0.59	0.73	0.10	BLQ	0.03	N/AP
D0999	168	0.54			0.03		
D1000	168	0.56			BLQ		
D1001	168	1.00			BLQ		
D1002	168	0.95			BLQ		

Kidney Results Repeat Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0619	168	NA			BLQ		
D0629	0	332.76	338.74	12.96	268.76	280.89	15.07
D0630	0	331.05			257.85		
D0631	0	375.80			325.20		
D0632	0	315.37			271.76		
D0645	2	210.00	238.51	9.52	81.67	75.05	7.61
D0646	2	246.56			93.24		
D0647	2	249.07			65.18		
D0648	2	248.41			60.12		
D0649	12	89.99	95.57	2.60	45.80	52.78	2.99
D0650	12	102.26			58.19		
D0651	12	93.55			57.31		
D0652	12	96.50			49.80		
D0653	24	54.11	55.48	1.64	46.67	47.51	2.77
D0654	24	52.48			41.42		
D0655	24	55.25			47.09		
D0656	24	60.09			54.88		
D0657	72	10.21	11.18	0.96	9.63	10.62	1.01
D0658	72	8.97			8.26		
D0659	72	12.39			11.98		
D0660	72	13.15			12.61		
D0661	120	6.64	5.73	0.63	2.45	2.34	0.53
D0662	120	6.38			3.73		
D0663	120	5.99			1.95		
D0664	120	3.89			1.23		
D0665	168	5.67	4.67	0.44	0.79	0.70	0.11
D0666	168	4.68			0.77		
D0667	168	4.11			0.89		
D0668	168	3.34			0.27		
D0669	168	5.53			0.78		

Kidney Results Single Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0952	168	NA			BLQ		
D0962	0	216.80	234.40	5.94	161.69	172.74	4.55
D0963	0	240.07			181.84		
D0964	0	242.55			178.26		
D0965	0	238.19			169.17		
D0978	2	171.56	161.17	5.19	49.71	54.22	1.68
D0979	2	146.87			53.83		
D0980	2	161.92			57.57		
D0981	2	164.33			55.74		
D0982	12	90.36	91.67	2.81	24.62	31.04	3.65
D0983	12	90.06			27.05		
D0984	12	99.71			41.19		
D0985	12	86.57			31.31		
D0986	24	66.79	73.73	4.81	33.14	37.28	3.20
D0987	24	87.80			46.63		
D0988	24	68.45			33.15		
D0989	24	71.88			36.19		
D0990	72	20.78	20.30	0.93	8.48	7.21	0.67
D0991	72	20.26			6.38		
D0992	72	17.84			5.75		
D0993	72	22.31			8.22		
D0994	120	9.53	8.87	0.47	1.71	1.49	0.13
D0995	120	8.17			1.52		
D0996	120	9.83			1.11		
D0997	120	7.94			1.60		
D0998	168	5.86	6.83	0.54	0.01	0.37	0.22
D0999	168	7.78			0.95		
D1000	168	5.39			0.01		
D1001	168	6.93			0.01		
D1002	168	8.20			0.85		

Testes Results Repeat Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0619	168	NA			BLQ		
D0629	0	128.56	132.10	1.87	58.50	62.83	1.57
D0630	0	134.58			65.49		
D0631	0	135.97			62.55		
D0632	0	129.26			64.77		
D0645	2	133.41	119.57	8.15	24.78	30.20	11.87
D0646	2	96.54			18.86		
D0647	2	128.26			12.19		
D0648	2	120.08			64.98		
D0649	12	29.02	27.13	1.02	4.58	5.81	1.63
D0650	12	28.74			4.64		
D0651	12	25.72			10.61		
D0652	12	25.03			3.40		
D0653	24	7.95	10.81	1.10	3.06	7.30	3.20
D0654	24	10.73			3.92		
D0655	24	11.23			5.42		
D0656	24	13.31			16.80		
D0657	72	3.15	3.80	0.42	1.03	1.43	0.29
D0658	72	3.10			1.21		
D0659	72	4.12			1.18		
D0660	72	4.84			2.30		
D0661	120	2.72	3.37	0.42	0.68	4.23	2.39
D0662	120	2.60			0.21		
D0663	120	4.34			10.38		
D0664	120	3.82			5.67		
D0665	168	2.26	2.07	0.18	0.19	0.88	0.29
D0666	168	2.62			1.70		
D0667	168	1.84			1.13		
D0668	168	1.55			1.10		
D0669	168	2.06			0.27		

Testes Results Single Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0952	168	NA			BLQ		
D0962	0	28.33	30.20	1.28	39.85	39.62	1.03
D0963	0	31.26			40.24		
D0964	0	27.88			36.74		
D0965	0	33.32			41.64		
D0978	2	26.77	25.82	0.58	5.27	6.11	0.55
D0979	2	26.69			7.17		
D0980	2	25.51			6.96		
D0981	2	24.31			5.05		
D0982	12	15.90	14.51	0.54	1.24	3.06	1.20
D0983	12	13.95			4.52		
D0984	12	14.77			5.66		
D0985	12	13.41			0.83		
D0986	24	6.65	6.52	0.33	1.18	1.92	0.68
D0987	24	5.91			0.94		
D0988	24	6.13			1.68		
D0989	24	7.39			3.91		
D0990	72	1.48	1.78	0.28	0.29	1.27	0.87
D0991	72	1.49			0.76		
D0992	72	2.63			3.86		
D0993	72	1.52			0.18		
D0994	120	1.12	1.38	0.26	BLQ	1.35	1.11
D0995	120	0.99			BLQ		
D0996	120	1.27			0.24		
D0997	120	2.14			2.46		
D0998	168	1.20	1.17	0.06	BLQ	0.29	0.19
D0999	168	1.29			0.48		
D1000	168	1.15			BLQ		
D1001	168	0.94			BLQ		
D1002	168	1.25			0.10		

Liver Results Repeat Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0619	168	NA			BLQ		
D0629	0	262.66	260.57	5.54	390.04	327.02	31.98
D0630	0	**113.02**			**370.15**		
D0631	0	268.96			286.09		
D0632	0	250.09			304.92		
D0645	2	237.57	206.30	15.65	6.95	5.40	0.65
D0646	2	176.06			5.75		
D0647	2	228.65			3.84		
D0648	2	182.93			5.08		
D0649	12	72.13	61.35	5.63	0.76	2.10	0.75
D0650	12	64.03			4.04		
D0651	12	45.51			2.52		
D0652	12	63.71			1.08		
D0653	24	28.90	32.58	1.62	0.30	0.38	0.09
D0654	24	30.93			0.22		
D0655	24	36.02			0.39		
D0656	24	34.47			0.61		
D0657	72	13.05	13.64	0.48	0.06	0.09	0.01
D0658	72	12.60			0.08		
D0659	72	14.47			0.11		
D0660	72	14.43			0.11		
D0661	120	8.31	6.95	0.54	0.04	0.05	0.01
D0662	120	7.07			0.06		
D0663	120	5.66			0.05		
D0664	120	6.77			0.06		
D0665	168	6.19	5.91	0.26	0.02	0.02	0.00
D0666	168	5.65			0.03		
D0667	168	6.68			0.03		
D0668	168	5.11			0.01		
D0669	168	5.90			0.02		

D0630, Extract wt incorrect, due to vial breaking in centrifuge, value not used to calculate mean

Liver Results Single Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0952	168	NA			BLQ		
D0962	0	181.41	182.74	0.72	83.81	86.35	6.70
D0963	0	181.66			68.41		
D0964	0	183.46			97.23		
D0965	0	184.42			95.97		
D0978	2	141.31	128.29	6.07	2.47	5.45	2.60
D0979	2	112.38			3.63		
D0980	2	126.97			2.48		
D0981	2	132.50			13.20		
D0982	12	84.67	88.24	2.60	0.83	1.10	0.31
D0983	12	85.37			0.97		
D0984	12	87.02			0.60		
D0985	12	95.90			2.01		
D0986	24	46.18	47.23	0.88	0.41	0.56	0.07
D0987	24	45.31			0.73		
D0988	24	48.44			0.62		
D0989	24	49.00			0.50		
D0990	72	14.78	12.55	0.80	BLQ	0.09	0.02
D0991	72	12.06			0.11		
D0992	72	10.99			BLQ		
D0993	72	12.38			0.08		
D0994	120	7.01	7.49	0.55	0.02	0.02	N/AP
D0995	120	6.29			BLQ		
D0996	120	8.86			BLQ		
D0997	120	7.82			BLQ		
D0998	168	7.51	6.43	0.44	BLQ	0.01	N/AP
D0999	168	6.40			BLQ		
D1000	168	6.22			BLQ		
D1001	168	4.93			0.01		
D1002	168	7.09			BLQ		

Lung Results Repeat Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0619	168	NA			BLQ		
D0629	0	161.18	155.12	4.53	109.94	126.69	7.46
D0630	0	152.73			140.76		
D0631	0	163.20			118.38		
D0632	0	143.36			137.68		
D0645	2	111.48	105.97	5.82	17.54	20.96	2.05
D0646	2	95.45			26.78		
D0647	2	119.70			18.75		
D0648	2	97.25			20.75		
D0649	12	28.95	27.30	1.25	9.74	10.75	0.97
D0650	12	28.01			12.62		
D0651	12	28.66			12.10		
D0652	12	23.59			8.53		
D0653	24	11.16	10.62	0.41	3.24	3.48	0.20
D0654	24	9.40			3.14		
D0655	24	10.84			4.04		
D0656	24	11.07			3.49		
D0657	72	3.84	4.44	0.26	0.27	0.31	0.02
D0658	72	4.24			0.28		
D0659	72	4.66			0.33		
D0660	72	5.03			0.36		
D0661	120	3.24	3.19	0.09	0.08	0.10	0.01
D0662	120	3.42			0.13		
D0663	120	2.99			0.12		
D0664	120	3.12			0.09		
D0665	168	3.53	2.64	0.32	0.08	0.07	0.01
D0666	168	3.05			0.07		
D0667	168	2.30			0.06		
D0668	168	1.69			0.05		
D0669	168	2.24			0.08		

Lung Results Single Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0952	168	NA			BLQ		
D0962	0	137.76	141.48	3.00	87.85	88.91	3.05
D0963	0	146.08			87.53		
D0964	0	135.02			82.84		
D0965	0	147.07			97.39		
D0978	2	96.39	92.94	7.86	27.45	33.22	8.17
D0979	2	102.51			48.33		
D0980	2	69.79			12.82		
D0981	2	103.07			44.28		
D0982	12	45.42	47.31	1.64	10.19	9.62	1.46
D0983	12	43.74			6.09		
D0984	12	50.79			13.14		
D0985	12	49.29			9.05		
D0986	24	26.85	24.21	1.98	3.33	2.84	0.35
D0987	24	27.05			3.19		
D0988	24	24.38			1.81		
D0989	24	18.56			3.02		
D0990	72	6.86	9.14	0.79	0.26	0.26	0.04
D0991	72	10.41			0.36		
D0992	72	9.93			0.17		
D0993	72	9.35			0.27		
D0994	120	4.93	7.31	1.44	BLQ	N/AP	N/AP
D0995	120	7.09			BLQ		
D0996	120	5.80			BLQ		
D0997	120	11.42			BLQ		
D0998	168	5.83	5.42	0.22	BLQ	N/AP	N/AP
D0999	168	4.68			BLQ		
D1000	168	5.80			BLQ		
D1001	168	5.14			BLQ		
D1002	168	5.64			BLQ		

Fat Results Repeat Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0619	168	NA			BLQ		
D0629	0	934.15	1193.89	138.03	2184.80	2646.92	286.44
D0630	0	1315.27			2297.31		
D0631	0	1001.48			2653.21		
D0632	0	1524.67			3452.37		
D0645	2	NS	1259.86	113.86	NS	3235.90	333.09
D0646	2	1295.12			3273.36		
D0647	2	1437.06			3793.18		
D0648	2	1047.39			2641.16		
D0649	12	1092.65	859.49	93.97	2575.74	1916.59	337.10
D0650	12	714.99			1454.76		
D0651	12	699.42			1227.83		
D0652	12	930.90			2408.01		
D0653	24	418.86	508.02	63.66	1402.27	1493.66	144.54
D0654	24	696.86			1833.58		
D0655	24	452.53			1588.40		
D0656	24	463.85			1150.40		
D0657	72	122.12	142.99	14.23	125.61	159.94	16.55
D0658	72	130.07			159.95		
D0659	72	134.84			149.55		
D0660	72	184.94			204.66		
D0661	120	88.98	63.52	9.78	72.07	46.30	11.59
D0662	120	68.56			59.22		
D0663	120	50.27			31.07		
D0664	120	46.26			22.86		
D0665	168	63.36	43.12	6.10	15.92	10.34	2.57
D0666	168	50.82			11.97		
D0667	168	30.64			14.16		
D0668	168	35.85			1.43		
D0669	168	34.94			8.21		

D0650 was run twice, the ug/g reported will be the average of the two results 1764.2

NS = No Sample 1145.3

Fat Results Single Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/g in sample	Radioactivity Avg Conc. ug Eq. HMDS/g / timepoint	std error of the mean	Parent Conc. ug HMDS/g	Parent Avg. Conc. ug HMDS/g / timepoint	std error of the mean
D0952	168	NA			BLQ		
D0962	0	1309.51	1530.82	127.62	1356.00	1527.93	115.53
D0963	0	1812.95			1793.51		
D0964	0	1320.08			1314.23		
D0965	0	1680.73			1647.98		
D0978	2	1372.25	1383.57	42.84	1344.18	1371.54	55.03
D0979	2	1359.47			1406.72		
D0980	2	1502.97			1498.62		
D0981	2	1299.59			1236.64		
D0982	12	725.32	920.38	82.46	721.98	911.38	85.28
D0983	12	1127.96			1127.66		
D0984	12	927.80			944.09		
D0985	12	900.46			851.78		
D0986	24	707.12	720.42	35.74	682.60	698.64	36.82
D0987	24	661.75			639.02		
D0988	24	823.94			805.72		
D0989	24	688.88			667.20		
D0990	72	263.13	231.57	20.54	182.25	154.79	21.60
D0991	72	249.18			186.05		
D0992	72	171.28			92.68		
D0993	72	242.68			158.17		
D0994	120	114.60	114.39	4.41	38.91	34.85	5.18
D0995	120	104.53			27.61		
D0996	120	112.54			25.32		
D0997	120	125.89			47.56		
D0998	168	82.48	83.75	4.02	3.63	7.55	2.95
D0999	168	85.13			18.21		
D1000	168	97.92			0.91		
D1001	168	73.71			6.67		
D1002	168	79.50			8.35		

Charcoal Results Repeat Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/hr in sample	Radioactivity Avg Conc. ug Eq. HMDS/hr / timepoint	std error of the mean	Parent Conc. ug HMDS/hr	Parent Avg. Conc. ug HMDS/hr / timepoint	std error of the mean
D0619	168	NA			BLQ		
D0665	1	5984.58	6059.26	401.97	6375.19	6660.97	359.43
D0666	1	5443.80			6083.66		
D0667	1	5935.24			6725.93		
D0668	1	7584.46			8020.78		
D0669	1	5348.21			6099.27		
D0665	2	2144.54	2116.36	68.45	2389.65	2448.21	57.53
D0666	2	1957.35			2357.65		
D0667	2	2058.05			2411.20		
D0668	2	2363.13			2675.21		
D0669	2	2058.71			2407.33		
D0665	4	1189.66	1301.20	69.42	1166.53	1336.17	67.92
D0666	4	1393.61			1495.58		
D0667	4	1103.63			1195.12		
D0668	4	1489.82			1469.86		
D0669	4	1329.31			1353.76		
D0665	6	791.42	851.76	33.15	751.85	855.98	47.19
D0666	6	881.30			928.45		
D0667	6	905.51			933.04		
D0668	6	755.68			729.66		
D0669	6	924.91			936.88		
D0665	12	406.43	408.92	15.30	412.87	431.87	19.06
D0666	12	417.38			465.14		
D0667	12	429.83			469.89		
D0668	12	351.85			367.10		
D0669	12	439.11			444.37		
D0665	24	198.49	167.36	10.38	250.54	255.10	36.52
D0666	24	170.56			224.96		
D0667	24	145.61			220.91		
D0668	24	178.74			394.92		
D0669	24	143.39			184.17		
D0665	48	100.42	81.80	7.24	135.25	117.36	6.87
D0666	48	87.13			129.58		
D0667	48	62.04			109.64		
D0668	48	91.40			115.23		
D0669	48	67.98			97.12		
D0665	72	37.75	31.47	2.49	57.44	50.43	3.18
D0666	72	36.00			57.85		
D0667	72	23.87			49.47		
D0668	72	30.50			41.87		
D0669	72	29.20			45.53		
D0665	96	17.17	13.43	1.33	26.78	23.14	2.22
D0666	96	15.69			27.18		
D0667	96	10.80			24.61		
D0668	96	10.36			15.05		
D0669	96	13.11			22.08		
D0665	120	8.67	6.53	0.80	33.87	15.56	4.74

Charcoal Results Repeat Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/hr in sample	Radioactivity Avg Conc. ug Eq. HMDS/hr / timepoint	std error of the mean	Parent Conc. ug HMDS/hr	Parent Avg. Conc. ug HMDS/hr / timepoint	std error of the mean
D0666	120	7.85			14.10		
D0667	120	5.29			12.02		
D0668	120	4.28			6.50		
D0669	120	6.57			11.31		
D0665	144	4.36	3.25	0.48	7.71	5.75	0.78
D0666	144	4.20			4.44		
D0667	144	2.75			7.10		
D0668	144	1.77			3.54		
D0669	144	3.18			5.93		
D0665	168	2.19	1.72	0.27	4.25	3.91	0.54
D0666	168	2.42			4.72		
D0667	168	1.62			4.89		
D0668	168	0.89			1.90		
D0669	168	1.48			3.78		

Charcoal Results Single Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/hr in sample	Radioactivity Avg Conc. ug Eq. HMDS/hr / timepoint	std error of the mean	Parent Conc. ug HMDS/hr	Parent Avg. Conc. ug HMDS/hr / timepoint	std error of the mean
D0952	168	NA			BLQ		
D0998	1	7567.10	6971.51	210.37	3591.54	3382.79	94.25
D0999	1	6641.93			3196.30		
D1000	1	6634.06			3388.07		
D1001	1	7397.97			3591.40		
D1002	1	6616.49			3146.67		
D0998	2	3027.90	2641.77	137.57	1434.17	1274.25	64.83
D0999	2	2486.28			1186.42		
D1000	2	2652.76			1280.71		
D1001	2	2817.52			1389.29		
D1002	2	2224.37			1080.64		
D0998	4	1801.02	1668.10	58.01	817.31	788.00	23.62
D0999	4	1507.09			721.97		
D1000	4	1555.09			739.96		
D1001	4	1760.77			834.94		
D1002	4	1716.54			825.80		
D0998	6	1073.60	1013.66	77.29	506.60	471.83	36.11
D0999	6	781.03			364.28		
D1000	6	892.78			413.84		
D1001	6	1205.50			563.56		
D1002	6	1115.39			510.89		
D0998	12	589.84	525.18	20.41	282.61	247.14	10.66
D0999	12	467.13			220.07		
D1000	12	513.96			239.34		
D1001	12	545.40			257.37		
D1002	12	509.57			236.29		
D0998	24	307.89	293.19	5.17	138.35	135.67	0.85
D0999	24	283.37			133.56		
D1000	24	285.93			136.13		
D1001	24	303.51			134.12		
D1002	24	285.27			136.18		
D0998	48	116.11	118.07	10.01	54.63	55.41	4.06
D0999	48	102.48			48.69		
D1000	48	156.94			71.07		
D1001	48	110.43			52.95		
D1002	48	104.40			49.70		
D0998	72	37.89	37.03	4.35	17.71	17.47	2.10
D0999	72	41.43			19.57		
D1000	72	20.26			9.45		
D1001	72	45.21			21.58		
D1002	72	40.34			19.05		
D0998	96	17.58	18.55	2.63	8.09	8.51	1.26
D0999	96	21.74			10.18		
D1000	96	8.71			3.77		
D1001	96	21.55			9.97		
D1002	96	23.16			10.56		
D0998	120	8.66	9.13	1.50	3.89	4.11	0.67

Charcoal Results Single Exposure

Animal ID	Time Point (hr)	Total Radioactivity Conc. ug Eq HMDS/hr in sample	Radioactivity Avg Conc. ug Eq. HMDS/hr / timepoint	std error of the mean	Parent Conc. ug HMDS/hr	Parent Avg. Conc. ug HMDS/hr / timepoint	std error of the mean
D0999	120	11.78			5.45		
D1000	120	3.57			1.65		
D1001	120	10.10			4.50		
D1002	120	11.55			5.04		
D0998	144	3.90	4.76	0.93	1.93	2.10	0.39
D0999	144	6.92			3.06		
D1000	144	1.61			0.75		
D1001	144	5.24			2.16		
D1002	144	6.12			2.59		
D0998	168	1.89	2.50	0.55	0.89	1.15	0.25
D0999	168	3.92			1.78		
D1000	168	0.77			0.35		
D1001	168	2.60			1.19		
D1002	168	3.33			1.56		

KOH Results Repeat Exposure

Animal ID	Time Point (hr)	Time Length KOH in Use (hr)	Group	Total DPM's	Cumulative DPM's	ug eq HMDS / hr Sample	Radioactivity ug eq. HMDS/hr Averages / timepoint	std error of the mean
D0619	24	24	1					
D0665	24	24	5	166284	166284	56.74	53.42	1.90
D0666	24	24	5	149278	149278	50.94		
D0667	24	24	5	159161	159161	54.31		
D0668	24	24	5	138917	138917	47.41		
D0669	24	24	5	169045	169045	57.69		
D0665	48	24	5	9364	175648	3.20	5.27	0.55
D0666	48	24	5	17794	167072	6.07		
D0667	48	24	5	15134	174295	5.16		
D0668	48	24	5	16882	155799	5.76		
D0669	48	24	5	18084	187129	6.17		
D0665	72	24	5	18163	193811	6.20	3.31	0.80
D0666	72	24	5	7542	174613	2.57		
D0667	72	24	5	6480	180775	2.21		
D0668	72	24	5	5076	160875	1.73		
D0669	72	24	5	11271	198401	3.85		
D0665	96	24	5	2893	196705	0.99	1.29	0.22
D0666	96	24	5	2530	177144	0.86		
D0667	96	24	5	6109	186884	2.08		
D0668	96	24	5	4164	165039	1.42		
D0669	96	24	5	3244	201645	1.11		
D0665	120	24	5	2662	199367	0.91	0.69	0.09
D0666	120	24	5	1461	178604	0.50		
D0667	120	24	5	2499	189383	0.85		
D0668	120	24	5	1432	166471	0.49		
D0669	120	24	5	2004	203649	0.68		
D0665	144	24	5	949	200315	0.32	0.26	0.08
D0666	144	24	5	1345	179949	0.46		
D0667	144	24	5	1127	190511	0.38		
D0668	144	24	5	308	166779	0.10		
D0669	144	24	5	127	203776	0.04		
D0665	168	24	5	1547	201862	0.53	0.56	0.14
D0666	168	24	5	1619	181568	0.55		
D0667	168	24	5	1540	192051	0.53		
D0668	168	24	5	2993	169772	1.02		
D0669	168	24	5	435	204211	0.15		

KOH Results Single Exposure

Animal ID	Time Point (hr)	Time Length KOH in Use (hr)	Group	Total DPM's	Cumulative DPM's	ug eq HMDS / hr Sample	Radioactivity ug eq. HMDS/hr Averages / timepoint	std error of the mean
D0952	24	24	7					
D0998	24	24	11	80986	80986	31.67	30.50	2.82
D0999	24	24	11	82916	82916	32.42		
D1000	24	24	11	65228	65228	25.51		
D1001	24	24	11	60047	60047	23.48		
D1002	24	24	11	100772	100772	39.40		
D0998	48	24	11	21763	102750	8.51	8.00	0.40
D0999	48	24	11	22074	104990	8.63		
D1000	48	24	11	22286	87514	8.71		
D1001	48	24	11	17167	77213	6.71		
D1002	48	24	11	18955	119727	7.41		
D0998	72	24	11	6935	109685	2.71	2.90	0.26
D0999	72	24	11	6114	111104	2.39		
D1000	72	24	11	7254	94769	2.84		
D1001	72	24	11	6787	84001	2.65		
D1002	72	24	11	9932	129659	3.88		
D0998	96	24	11	3951	113636	1.54	1.62	0.14
D0999	96	24	11	5225	116329	2.04		
D1000	96	24	11	3867	98635	1.51		
D1001	96	24	11	3089	87090	1.21		
D1002	96	24	11	4535	134194	1.77		
D0998	120	24	11	2281	115917	0.89	0.93	0.09
D0999	120	24	11	2060	118389	0.81		
D1000	120	24	11	3150	101785	1.23		
D1001	120	24	11	1762	88852	0.69		
D1002	120	24	11	2620	136814	1.02		
D0998	144	24	11	1679	117596	0.66	1.03	0.16
D0999	144	24	11	3997	122386	1.56		
D1000	144	24	11	1890	103675	0.74		
D1001	144	24	11	2958	91810	1.16		
D1002	144	24	11	2594	139408	1.01		
D0998	168	24	11	1747	119343	0.68	0.57	0.09
D0999	168	24	11	2162	124548	0.85		
D1000	168	24	11	1270	104945	0.50		
D1001	168	24	11	1102	92911	0.43		
D1002	168	24	11	957	140365	0.37		

Feces Results Repeat Exposure

Animal ID	Time Point (hr)	Group	Total DPM's	Cumulative DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0619	24	1					
D0665	12	5	3471	3471	32.06	85.88	32.03
D0666	12	5	17438	17438	165.09		
D0667	12	5	28182	28182	110.73		
D0668	12	5	No Sample	No Sample	No Sample		
D0669	12	5	4027	4027	35.63		
D0665	24	5	48747	52218	203.73	216.49	12.32
D0666	24	5	89648	107086	250.74		
D0667	24	5	64097	92280	186.13		
D0668	24	5	51930	51930	201.74		
D0669	24	5	49138	53165	240.13		
D0665	48	5	30666	82884	39.79	49.66	5.60
D0666	48	5	28655	135741	38.75		
D0667	48	5	60148	152427	63.22		
D0668	48	5	48449	100379	63.30		
D0669	48	5	37600	90765	43.22		
D0665	72	5	17199	100083	22.49	15.81	3.25
D0666	72	5	8969	144710	9.76		
D0667	72	5	23768	176195	23.07		
D0668	72	5	6943	107322	7.06		
D0669	72	5	13845	104611	16.65		
D0665	96	5	4201	104284	5.63	9.02	4.07
D0666	96	5	4130	148840	4.99		
D0667	96	5	27107	203302	25.25		
D0668	96	5	4324	111647	5.41		
D0669	96	5	2176	106787	3.80		
D0665	120	5	3221	107504	4.42	5.11	1.34
D0666	120	5	2201	151041	2.67		
D0667	120	5	6235	209537	5.86		
D0668	120	5	3168	114814	2.71		
D0669	120	5	7066	113853	9.91		
D0665	144	5	3547	111051	3.81	3.26	0.37
D0666	144	5	2517	153558	2.52		
D0667	144	5	3358	212896	3.47		
D0668	144	5	2260	117075	2.28		
D0669	144	5	3896	117748	4.21		
D0665	168	5	1113	112164	1.69	2.99	0.84
D0666	168	5	3135	156692	2.59		
D0667	168	5	3809	216704	3.47		
D0668	168	5	5097	122171	5.96		
D0669	168	5	1097	118845	1.24		

Feces Results Single Exposure

Animal ID	Time Point (hr)	Group	Total DPM's	Cumulative DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0952	24	7					
D0998	6	11	305	305	16.59	27.43	10.84
D0999	6	11	No Sample	No Sample	No Sample		
D1000	6	11	No Sample	No Sample	No Sample		
D1001	6	11	No Sample	No Sample	No Sample		
D1002	6	11	1015	1015	38.27		
D0998	12	11	No Sample	No Sample	No Sample	203.58	N/AP
D0999	12	11	No Sample	No Sample	No Sample		
D1000	12	11	8272	8272	203.58		
D1001	12	11	No Sample	No Sample	No Sample		
D1002	12	11	No Sample	No Sample	No Sample		
D0998	24	11	62055	62359	349.84	259.44	30.90
D0999	24	11	21475	21475	155.76		
D1000	24	11	41818	50090	256.83		
D1001	24	11	51280	51280	272.17		
D1002	24	11	46290	47306	262.61		
D0998	48	11	26624	88983	47.89	57.08	6.35
D0999	48	11	27466	48940	46.48		
D1000	48	11	16694	66783	80.32		
D1001	48	11	31767	83047	49.77		
D1002	48	11	33247	80552	60.96		
D0998	72	11	3800	92784	5.85	12.11	4.26
D0999	72	11	17402	66343	28.77		
D1000	72	11	7007	73790	7.03		
D1001	72	11	6529	89576	7.74		
D1002	72	11	6968	87520	11.15		
D0998	96	11	1139	93923	1.76	10.09	6.60
D0999	96	11	29492	95835	34.90		
D1000	96	11	120	73910	0.18		
D1001	96	11	777	90353	1.06		
D1002	96	11	8765	96285	12.53		
D0998	120	11	905	94827	1.18	2.23	1.29
D0999	120	11	5138	100973	7.05		
D1000	120	11	1370	75280	2.70		
D1001	120	11	174	90527	0.23		
D1002	120	11	0	96285	0.00		
D0998	144	11	0	94827	0.00	2.03	1.25
D0999	144	11	0	100973	0.00		
D1000	144	11	2836	78116	4.63		
D1001	144	11	4092	94619	5.51		
D1002	144	11	0	96285	0.00		
D0998	168	11	0	94827	0.00	0.96	0.96
D0999	168	11	4352	105325	4.82		
D1000	168	11	0	78116	0.00		
D1001	168	11	0	94619	0.00		
D1002	168	11	0	96285	0.00		

Urine Results Repeat Exposure

Animal ID	Time Point (hr)	Group	Total DPM's	Cumulative DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0619	24	1					
D0665	12	5	4025538	4025538	5981.78	5026.10	362.93
D0666	12	5	3292002	3292002	5099.68		
D0667	12	5	4129155	4129155	3829.57		
D0668	12	5	4057733	4057733	4742.34		
D0669	12	5	4427784	4427784	5477.14		
D0665	24	5	1274830	5300369	2053.75	1638.51	184.50
D0666	24	5	1144669	4436670	1767.04		
D0667	24	5	717356	4846511	946.35		
D0668	24	5	934131	4991864	1683.25		
D0669	24	5	851441	5279225	1742.15		
D0665	48	5	512707	5813075	421.25	387.04	20.70
D0666	48	5	492847	4929518	394.69		
D0667	48	5	418812	5265323	315.29		
D0668	48	5	539552	5531416	431.51		
D0669	48	5	461909	5741135	372.48		
D0665	72	5	180846	5993922	125.83	109.30	13.43
D0666	72	5	169775	5099292	152.07		
D0667	72	5	89341	5354664	77.42		
D0668	72	5	132976	5664392	88.14		
D0669	72	5	116609	5857743	103.07		
D0665	96	5	75137	6069059	60.21	51.44	5.00
D0666	96	5	87352	5186645	64.13		
D0667	96	5	42429	5397093	41.13		
D0668	96	5	56428	5720820	39.01		
D0669	96	5	61129	5918872	52.69		
D0665	120	5	39728	6108786	30.71	28.03	2.70
D0666	120	5	43926	5230571	37.17		
D0667	120	5	26014	5423107	25.00		
D0668	120	5	32479	5753298	21.71		
D0669	120	5	33266	5952138	25.57		
D0665	144	5	22451	6131237	19.20	18.31	1.51
D0666	144	5	25670	5256240	23.25		
D0667	144	5	17317	5440424	15.29		
D0668	144	5	19683	5772982	15.02		
D0669	144	5	22860	5974998	18.79		
D0665	168	5	18411	6149648	12.11	12.02	1.31
D0666	168	5	16622	5272863	17.04		
D0667	168	5	11224	5451648	10.40		
D0668	168	5	12849	5785831	10.52		
D0669	168	5	13299	5988297	10.02		

Urine Results Single Exposure

Animal ID	Time Point (hr)	Group	Total DPM's	Cumulative DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0952	24	7					
D0998	6	11	563694	563694	2139.59	2187.41	161.28
D0999	6	11	250591	250591	1859.74		
D1000	6	11	377619	377619	2343.42		
D1001	6	11	305961	305961	1871.62		
D1002	6	11	474912	474912	2722.68		
D0998	12	11	820231	1383926	2958.93	3347.98	129.56
D0999	12	11	963371	1213962	3428.77		
D1000	12	11	941410	1319029	3560.74		
D1001	12	11	1086155	1392116	3142.75		
D1002	12	11	954987	1429899	3648.71		
D0998	24	11	514043	1897969	2307.68	2200.11	74.83
D0999	24	11	547081	1761043	2059.21		
D1000	24	11	589593	1908622	2297.74		
D1001	24	11	738662	2130777	1982.24		
D1002	24	11	516410	1946309	2353.66		
D0998	48	11	545162	2443131	740.73	627.37	57.44
D0999	48	11	513292	2274335	683.85		
D1000	48	11	618991	2527613	501.59		
D1001	48	11	555157	2685934	476.58		
D1002	48	11	646568	2592877	734.07		
D0998	72	11	147259	2590390	153.59	153.58	11.95
D0999	72	11	166286	2440622	188.73		
D1000	72	11	119955	2647568	138.82		
D1001	72	11	172092	2858026	118.93		
D1002	72	11	160511	2753388	167.82		
D0998	96	11	57594	2647984	72.65	68.19	8.03
D0999	96	11	58790	2499411	83.15		
D1000	96	11	44324	2691892	44.40		
D1001	96	11	77327	2935353	55.05		
D1002	96	11	74934	2828322	85.70		
D0998	120	11	39222	2687206	39.70	35.92	4.82
D0999	120	11	36936	2536347	44.78		
D1000	120	11	21495	2713387	21.49		
D1001	120	11	39322	2974675	27.82		
D1002	120	11	44654	2872976	45.82		
D0998	144	11	22877	2710083	26.91	22.76	3.20
D0999	144	11	22235	2558582	28.29		
D1000	144	11	17426	2730813	12.92		
D1001	144	11	23947	2998622	17.37		
D1002	144	11	29023	2901999	28.30		
D0998	168	11	14932	2725015	18.38	14.87	1.74
D0999	168	11	11586	2570168	17.25		
D1000	168	11	9691	2740504	9.29		
D1001	168	11	15986	3014608	12.34		
D1002	168	11	16722	2918721	17.07		

THF Cage Rinse Results Repeat Exposure

Animal ID	Time Point	Group	Total DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0619	168	1				
D0665	168	5	1989	1.45	1.44	0.17
D0666	168	5	450	1.76		
D0667	168	5	1302	0.95		
D0668	168	5	1451	1.15		
D0669	168	5	3375	1.87		

Hexane Cage Rinse Results Repeat Exposure

Animal ID	Time Point	Group	Total DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0619	168	1				
D0665	168	5	150	0.17	0.19	0.06
D0666	168	5	217	0.15		
D0667	168	5	120	0.08		
D0668	168	5	399	0.42		
D0669	168	5	247	0.13		

THF Cage Rinse Results Single Exposure

Animal ID	Time Point	Group	Total DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0952	168	7				
D0998	168	11	2195	0.35	0.40	0.05
D0999	168	11	1715	0.45		
D1000	168	11	1620	0.24		
D1001	168	11	1873	0.51		
D1002	168	11	2553	0.47		

Hexane Cage Rinse Results Single Exposure

Animal ID	Time Point	Group	Total DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0952	168	7				
D0998	168	11	59	0.02	0.05	0.02
D0999	168	11	180	0.10		
D1000	168	11	23	0.01		
D1001	168	11	62	0.02		
D1002	168	11	306	0.09		

Cone Rinse Results Repeat Exposure

Animal ID	Time Point	Group	Total DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0665	168	5	58994	23.45		
D0666	168	5	448577	137.08	64.24	28.19
D0667	168	5	5157	2.39		
D0668	168	5	165804	71.85		
D0669	168	5	143183	45.63		

Cone Rinse Results Single Exposure

Animal ID	Time Point	Group	Total DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0998	168	11	34084	12.07		
D0999	168	11	121431	45.22	26.83	7.97
D1000	168	11	54730	15.11		
D1001	168	11	130972	35.02		
D1002	168	11	44957	11.99		

Excreta Carcass Results Repeat Exposure

Animal ID	Time Point	Group	Total DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0619	168	1				
D0665	168	5	159355	6.29	9.67	1.91
D0666	168	5	312974	12.36		
D0667	168	5	191922	7.41		
D0668	168	5	388854	15.87		
D0669	168	5	167288	6.41		

Excreta Carcass Results Single Exposure

Animal ID	Time Point	Group	Total DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0952	168	7				
D0998	168	11	242018	11.74	10.79	0.33
D0999	168	11	229817	10.73		
D1000	168	11	205488	9.75		
D1001	168	11	232991	10.59		
D1002	168	11	247669	11.15		

Body Burden Carcass Results Repeat Exposure

Animal ID	Time Point	Group	Total DPM's
D0620	0	2	
D0621	0	3	5424487
D0622	0	3	8424159
D0623	0	3	7812643
D0624	0	3	5872022

Glove Waste Results Repeat Exposure

Animal ID	Time Point	Group	Total DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0620	0	2				
D0621	0	3	60025.71	3.81	6.11	2.36
D0622	0	3	204975.48	13.01		
D0623	0	3	40224.50	2.55		
D0624	0	3	79686.86	5.06		

Body Burden Carcass Results Single Exposure

Animal ID	Time Point	Group	Total DPM's
D0953	0	8	
D0954	0	9	4882771
D1003	0	9	5342350
D0956	0	9	5939822
D1004	0	9	5113324

Glove Waste Results Single Exposure

Animal ID	Time Point	Group	Total DPM's	ug eq HMDS / g Sample	Radioactivity ug eq. HMDS/g Averages / timepoint	std error of the mean
D0954	0	9	30524.21	2.10		
D1003	0	9	54549.30	4.01	4.13	0.25
D0956	0	9	53182.58	3.78		
D1004	0	9	61725.52	4.62		

Carcass
Males

Group	Animal Number	Sample Time (hr)	Dose (DPM's)	Terminal Body Wt (g)	Respiratory Minute Volume (ml/min.)**	Volume of respired air (L)	Calculated achieved dose uCi/animal	Total Activity (DPM)	Total Activity from glove waste (DPM)	Total from carcass and glove waste (DPM)	Body Burden Dose (uCi/kg)	% of Achieved Dose Retained	uCi in Sample
2	D0620	0	0										
3	D0621	0	176435516	204.0	113.4	40.8	79.5	5424487	60026	5484513	12.110	3.11	2.47
3	D0622	0	180248938	209.9	115.8	41.7	81.2	8424159	204975	8629135	18.518	4.79	3.89
3	D0623	0	180956933	211.0	116.3	41.9	81.5	7812643	40225	7852867	16.765	4.34	3.54
3	D0624	0	190901049	226.6	122.6	44.2	86.0	5872022	79687	5951708	11.831	3.12	2.68
		average	182135609	212.9	117.0	42.1	82.0			6979556	14.8	3.8	3.1
		SD	6171785.4	9.65	3.97	1.43	2.78			1502820.3	3.35	0.86	0.68

Achieved Dose Calculation = $\dfrac{\text{Respiratory Minute Volume (mL/min.)** x exposure duration (min.) x achieved mean}}{\text{}^{14}\text{C-HMDS vapor concentration*** (mg/L) x specific activity of dosing solution (dpm/ug)}}$

Exposure Duration = 360 minutes
Achieved Mean 14C-HMDS vapor Concentration*** = 35.41 mg/L
Specific Activity of Dosing Solution = 122.1 dpm/ug 0.055 mCi/g

* Background subtract comes from DPM/g of aliquot for group 2 (control) carcasses.

** Respiratory Minute Volume = 2.1(mL/min.) x BW (grams)$^{0.75}$

***Achieved Mean 14C-HMDS vapor Concentration Calculation= 5365ppm (mean inhalation conc.) / 151.5ppm

151.5ppm = 1mg/L = 24.6 (L/mol) / molecular weight HMDS (162380mg/mol)

Carcass
Males

Group	Animal Number	Sample Time (hr)	Dose (DPM's)	Terminal Body Wt (g)	Respiratory Minute Volume (ml/min.)**	Volume of respired air (L)	Calculated achieved dose uCi/animal	Total Activity (DPM)	Total Activity from glove waste (DPM)	Total from carcass and glove waste (DPM)	Body Burden Dose (uCi/kg)	% of Achieved Dose Retained	uCi in Sample
8	D0953	0	0										
9	D0954	0	142405417	202.5	112.7	40.6	64.1	4882771	30524	4913295	10.929	3.45	2.21
9	D1003	0	150608262	218.2	119.2	42.9	67.8	5342350	54549	5396899	11.141	3.58	2.43
9	D0956	0	150452934	217.9	119.1	42.9	67.8	5939822	53183	5993004	12.389	3.98	2.70
9	D1004	0	147022012	211.3	116.4	41.9	66.2	5113324	61726	5175049	11.032	3.52	2.33
		Average	147622156	212.5	116.9	42.1	66.5			5369562	11.4	3.6	2.4
		SD	3851609.0	7.37	3.05	1.10	1.73			460232.7	0.68	0.24	0.21

Achieved Dose Calculation = **Respiratory Minute Volume (mL/min.)** x exposure duration (min.) x achieved mean ^{14}C-HMDS vapor concentration*** (mg/L) x specific activity of dosing solution (dpm/ug)**

Exposure Duration = 360 minutes
Achieved Mean 14C-HMDS vapor Concentration*** = 32.9300 mg/L
Specific Activity of Dosing Solution = 106.5600 dpm/ug 0.048 mCi/g

* Background subtract comes from DPM/g of aliquot for group 2 (control) carcasses.

** Respiratory Minute Volume = 2.1(mL/min.) x BW (grams)$^{0.75}$

***Achieved Mean 14C-HMDS vapor Concentration Calculation= 4989ppm (mean inhalation conc.) / 151.5ppm

151.5ppm = 1mg/L = 24.6 (L/mol) / molecular weight HMDS (162380mg/mol)

Per Matrix Individual Test Subject DPM's

Animal ID	Blood	Carcass	Cone Rinse	Expired Volatiles	Feces	Hexane Rinse	KOH	THF Rinse	Urine	Tissues*	Total DPM's	Percent Body Burden
D0665	55	159355	58994	2564726	112164	150	201862	1989	6149648	14439	9263382	132.7
D0666	59	312974	448577	2464115	156692	217	181568	450	5272863	10931	8848447	126.8
D0667	45	191922	5157	2306580	216704	120	192051	1302	5451648	11697	8377227	120.0
D0668	51	388854	165804	2690527	122171	399	169772	1451	5785831	9266	9334126	133.7
D0669	49	167288	143183	2342764	118845	247	204211	3375	5988297	12365	8980623	128.7
Mean	52	244079	164343	2473742	145315	227	189893	1713	5729657	11740	8960761	128.4
SD	5.5	101860.1	171520.6	158481.1	43477.4	108.9	14379.4	1080.5	364826.2	1900.9	382263.8	5.5
SEM	2.5	45553.2	76706.3	70874.9	19443.7	48.7	6430.7	483.2	163155.2	850.1	170953.6	2.4
%SEM Recovery	0.00	0.51	0.86	0.79	0.22	0.00	0.07	0.01	1.82	0.01	1.9	
%SEM Body Burden	0.00	0.65	1.10	1.02	0.28	0.00	0.09	0.01	2.34	0.01	2.4	
% Recovery	0.00	2.72	1.83	27.61	1.62	0.00	2.12	0.02	63.94	0.13	100.0	
% Body Burden	0.00	3.50	2.35	35.44	2.08	0.00	2.72	0.02	82.09	0.17	128.4	

Body Burden Response (DPM's) = 6979556
* equals total from tissues listed below

Animal ID	Brain Extract	Brain Solub.	Kidney Extract	Kidney Solub.	Liver Extract	Liver Solub.	Lung Extract	Lung Solub.	Peri-renal Fat Extract	Peri-renal Fat Solub.	Testes Extract	Testes Solub.
D0665	69	124	240	880	381	6454	242	133	4706	625	156	430.0
D0666	98	76	349	562	186	5652	273	66	2619	246	288	516.4
D0667	111	196	168	663	1636	5567	153	99	2192	309	72	533.1
D0668	76	159	336	378	263	4945	240	0	1985	300	151	432.0
D0669	41	142	181	996	938	5908	235	34	2658	618	116	499.6
Mean	79	139	255	696	681	5705	229	66	2832	419	157	482.2
SD	27.0	44.5	84.7	247.0	609.6	547.9	44.9	52.4	1085.6	185.7	80.7	48.2
SEM	12.1	19.9	37.9	110.5	272.6	245.0	20.1	23.4	485.5	83.0	36.1	21.6
%SEM Recovery	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00
%SEM Body Burden	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00
% Recovery	0.00	0.00	0.00	0.01	0.01	0.06	0.00	0.00	0.03	0.00	0.00	0.01
% Body Burden	0.00	0.00	0.00	0.01	0.01	0.08	0.00	0.00	0.04	0.01	0.00	0.01

Per Matrix Individual Test Subject DPM's

Animal ID	Blood	Carcass	Cone Rinse	Expired Volatiles	Feces	Hexane Rinse	KOH	THF Rinse	Urine	Tissues*	Total DPM's	Percent Body Burden
D0998	43	242018	34084	2988221	94827	59	119343	2195	2725015	12071	6217875	115.8
D0999	37	229817	121431	2602849	105325	180	124548	1715	2570168	10218	5766289	107.4
D1000	48	205488	54730	2696185	78116	23	104945	1620	2740504	11491	5893150	109.8
D1001	31	232991	130972	2956600	94619	62	92911	1873	3014608	13201	6537869	121.8
D1002	30	247669	44957	2719309	96285	306	140365	2553	2918721	15169	6185365	115.2
Mean	38	231597	77235	2792633	93834	126	116422	1991	2793803	12430	6120110	114.0
SD	7.8	16230.4	45418.4	170173.7	9832.6	116.7	18250.2	382.6	174602.9	1870.9	302092.2	5.6
SEM	3.5	7258.5	20311.7	76104.0	4397.3	52.2	8161.7	171.1	78084.8	836.7	135099.7	2.5
%SEM Recovery	0.00	0.12	0.33	1.24	0.07	0.00	0.13	0.00	1.28	0.01	2.2	
%SEM Body Burden	0.00	0.14	0.38	1.42	0.08	0.00	0.15	0.00	1.45	0.02	2.5	
% Recovery	0.00	3.78	1.26	45.63	1.53	0.00	1.90	0.03	45.65	0.20	100.0	
% Body Burden	0.00	4.31	1.44	52.01	1.75	0.00	2.17	0.04	52.03	0.23	114.0	

Body Burden Response (DPM's) = 5369562
* equals total from tissues listed below

Animal ID	Brain Extract	Brain Solub.	Kidney Extract	Kidney Solub.	Liver Extract	Liver Solub.	Lung Extract	Lung Solub.	Peri-renal Fat Extract	Peri-renal Fat Solub.	Testes Extract	Testes Solub.
D0998	109	0	485	475	1299	4610	64	477	3799	408	54	290.6
D0999	104	0	692	605	471	4386	31	422	2923	185	51	348.7
D1000	109	0	445	542	493	4645	82	429	4060	347	43	295.9
D1001	158	13	674	647	95	4643	0	502	5422	740	65	240.7
D1002	180	0	773	790	630	6074	160	476	5041	657	58	330.9
Mean	132	3	614	612	598	4871	67	461	4249	468	54	301.4
SD	34.6	6.0	141.7	118.8	439.4	680.7	60.3	34.2	1000.0	228.1	8.3	41.6
SEM	15.5	2.7	63.4	53.1	196.5	304.4	27.0	15.3	447.2	102.0	3.7	18.6
%SEM Recovery	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00
%SEM Body Burden	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.01	0.00	0.00	0.00
% Recovery	0.00	0.00	0.01	0.01	0.01	0.08	0.00	0.01	0.07	0.01	0.00	0.00
% Body Burden	0.00	0.00	0.01	0.01	0.01	0.09	0.00	0.01	0.08	0.01	0.00	0.01

HPLC URINE ANALYSIS

Animal ID	Time Point	Group / Sex	NET AREA CPM											Total CPMs
			hydroxymethyl-dimethylsilanol	Dimethyl-silanediol	(1,3-bis (hydroxymethyl) tetramethyl-disiloxane)	Unknown	Unknown	Trimethyl silanol	Unknown	Unknown	Unknown	pentamethyl-disiloxanol	hydroxymethyl-pentamethyl-disiloxane	
			~5.3min. Retention time metabolite	**~13.5min.** Retention time metabolite	**~25.0min.** Retention time metabolite	**~26.5min.** Retention time metabolite	**~29.0min.** Retention time metabolite	**~32.2min.** Retention time metabolite	**~32.9min.** Retention time metabolite	**~33.9min.** Retention time metabolite	**~37.0min.** Retention time metabolite	**~38.4min.** Retention time metabolite	**~39.2min.** Retention time metabolite	
D0665	12	5/M	11296	8991	27423	6133	5764	7507	1901	1397	0	334	768	71514
			16%	*13%*	*38%*	*9%*	*8%*	*10%*	*3%*	*2%*	*0%*	*0%*	*1%*	
D0666	12	5/M	11102	6620	21154	5080	5858	5521	1825	1213	0	0	407	58780
			19%	*11%*	*36%*	*9%*	*10%*	*9%*	*3%*	*2%*	*0%*	*0%*	*1%*	
D0667	12	5/M	7899	5058	11768	3508	4144	4102	970	649	0	0	928	39026
			20%	*13%*	*30%*	*9%*	*11%*	*11%*	*2%*	*2%*	*0%*	*0%*	*2%*	
D0668	12	5/M	8084	5898	17861	3647	6472	5527	1340	917	358	404	912	51420
			16%	*11%*	*35%*	*7%*	*13%*	*11%*	*3%*	*2%*	*1%*	*1%*	*2%*	
D0669	12	5/M	11108	7726	23296	4984	4936	6337	1601	1155	0	0	670	61813
			18%	*12%*	*38%*	*8%*	*8%*	*10%*	*3%*	*2%*	*0%*	*0%*	*1%*	
		Mean	***18%***	***12%***	***35%***	***8%***	***10%***	***10%***	***3%***	***2%***	***0%***	***0%***	***1%***	
		SD	***2.0%***	***0.7%***	***3.2%***	***0.7%***	***1.9%***	***0.5%***	***0.2%***	***0.2%***	***0.3%***	***0.4%***	***0.7%***	
D0665	24	5/M	8012	6279	8928	0	620	1269	343	0	0	0	0	25451
			31%	*25%*	*35%*	*0%*	*2%*	*5%*	*1%*	*0%*	*0%*	*0%*	*0%*	
D0666	24	5/M	6029	4371	5407	1644	0	1074	360	0	338	0	0	19223
			31%	*23%*	*28%*	*9%*	*0%*	*6%*	*2%*	*0%*	*2%*	*0%*	*0%*	
D0667	24	5/M	2830	2517	2352	0	0	0	0	0	0	0	0	7699
			37%	*33%*	*31%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	
D0668	24	5/M	5644	4596	4832	2910	737	1152	0	0	0	0	0	19871
			28%	*23%*	*24%*	*15%*	*4%*	*6%*	*0%*	*0%*	*0%*	*0%*	*0%*	
D0669	24	5/M	6969	5478	4188	2492	0	688	380	0	0	0	0	20195
			35%	*27%*	*21%*	*12%*	*0%*	*3%*	*2%*	*0%*	*0%*	*0%*	*0%*	
		Mean	***33%***	***26%***	***28%***	***7%***	***1%***	***4%***	***1%***	***0%***	***0%***	***0%***	***0%***	
		SD	***3.2%***	***4.1%***	***5.5%***	***6.8%***	***1.7%***	***2.4%***	***1.0%***	***0.0%***	***0.8%***	***0.0%***	***0.0%***	

HPLC URINE ANALYSIS

Animal ID	Time Point	Group / Sex	NET AREA CPM											Total CPMs
			hydroxymethyl-dimethylsilanol	Dimethyl-silanediol	(1,3-bis (hydroxymethyl) tetramethyldisiloxane)	Unknown	Unknown	Unknown	Trimethyl silanol	Unknown	Unknown	pentamethyl-disiloxanol	Unknown	
			~5.3min. Retention time metabolite	**~13.5min.** Retention time metabolite	**~25.0min.** Retention time metabolite	**~26.5min.** Retention time metabolite	**~29.0min.** Retention time metabolite	**~31.3min.** Retention time metabolite	**~32.2min.** Retention time metabolite	**~32.9min.** Retention time metabolite	**~33.9min.** Retention time metabolite	**~38.4min.** Retention time metabolite	**back-ground counts**	
D0998	0-6	11/M	1878	3121	0	15691	321	0	2694	0	0	308	390	24403
			8%	*13%*	*0%*	*64%*	*1%*	*0%*	*11%*	*0%*	*0%*	*1%*	*2%*	
D0999	0-6	11/M	1646	2302	0	10976	719	474	2225	0	0	0	0	18342
			9%	*13%*	*0%*	*60%*	*4%*	*3%*	*12%*	*0%*	*0%*	*0%*	*0%*	
D1000	0-6	11/M	2429	3013	0	15378	0	0	3797	521	439	0	0	25577
			9%	*12%*	*0%*	*60%*	*0%*	*0%*	*15%*	*2%*	*2%*	*0%*	*0%*	
D1001	0-6	11/M	1491	2785	0	12357	0	899	2172	0	0	316	0	20020
			7%	*14%*	*0%*	*62%*	*0%*	*4%*	*11%*	*0%*	*0%*	*2%*	*0%*	
D1002	0-6	11/M	3508	3857	0	18149	0	0	5106	0	344	0	0	30964
			11%	*12%*	*0%*	*59%*	*0%*	*0%*	*16%*	*0%*	*1%*	*0%*	*0%*	
		Mean	**9%**	**13%**	**0%**	**61%**	**1%**	**1%**	**13%**	**0%**	**1%**	**1%**	**0%**	
		SD	**2%**	**1%**	**0%**	**2%**	**2%**	**2%**	**2%**	**1%**	**1%**	**1%**	**1%**	
D0998	6-12	11/M	4838	4743	6086	12676	370	0	2746	516	810	0	0	32785
			15%	*14%*	*19%*	*39%*	*1%*	*0%*	*8%*	*2%*	*2%*	*0%*	*0%*	
D0999	6-12	11/M	5477	5652	9150	13012	0	640	2744	944	684	0	356	38659
			14%	*15%*	*24%*	*34%*	*0%*	*2%*	*7%*	*2%*	*2%*	*0%*	*1%*	
D1000	6-12	11/M	5241	5473	10631	12223	0	0	4367	717	640	0	0	39292
			13%	*14%*	*27%*	*31%*	*0%*	*0%*	*11%*	*2%*	*2%*	*0%*	*0%*	
D1001	6-12	11/M	5312	4675	7946	12393	0	0	3501	657	598	0	0	35082
			15%	*13%*	*23%*	*35%*	*0%*	*0%*	*10%*	*2%*	*2%*	*0%*	*0%*	
D1002	6-12	11/M	7103	6149	11343	11605	0	524	3162	970	731	0	643	42230
			17%	*15%*	*27%*	*27%*	*0%*	*1%*	*7%*	*2%*	*2%*	*0%*	*2%*	
		Mean	**15%**	**14%**	**24%**	**33%**	**0%**	**1%**	**9%**	**2%**	**2%**	**0%**	**0%**	
		SD	**1%**	**1%**	**3%**	**4%**	**1%**	**1%**	**2%**	**0%**	**0%**	**0%**	**1%**	
D0998	12-24	11/M	6490	5992	0	12983	0	0	1462	653	0	0	0	27580
			24%	*22%*	*0%*	*47%*	*0%*	*0%*	*5%*	*2%*	*0%*	*0%*	*0%*	
D0999	12-24	11/M	5558	5089	0	10310	0	0	993	0	0	0	0	21950
			25%	*23%*	*0%*	*47%*	*0%*	*0%*	*5%*	*0%*	*0%*	*0%*	*0%*	
D1000	12-24	11/M	6218	5144	0	11957	340	0	1339	623	0	0	0	25621
			24%	*20%*	*0%*	*47%*	*1%*	*0%*	*5%*	*2%*	*0%*	*0%*	*0%*	
D1001	12-24	11/M	5585	4497	0	10708	604	0	1014	0	0	0	0	22408
			25%	*20%*	*0%*	*48%*	*3%*	*0%*	*5%*	*0%*	*0%*	*0%*	*0%*	
D1002	12-24	11/M	6114	5196	0	11006	442	0	602	505	0	0	0	23865
			26%	*22%*	*0%*	*46%*	*2%*	*0%*	*3%*	*2%*	*0%*	*0%*	*0%*	
		Mean	**25%**	**21%**	**0%**	**47%**	**1%**	**0%**	**4%**	**1%**	**0%**	**0%**	**0%**	
		SD	**1%**	**1%**	**0%**	**1%**	**1%**	**0%**	**1%**	**1%**	**0%**	**0%**	**0%**	

Brain Repeat Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0629	0	4	319.05	64.36	383.41	83.21
D0630	0	4	272.70	44.10	316.80	86.08
D0631	0	4	311.13	57.20	368.33	84.47
D0632	0	4	273.48	44.30	317.78	86.06
D0645	2	4	175.06	36.97	212.03	82.56
D0646	2	4	124.86	26.30	151.16	82.60
D0647	2	4	163.77	34.83	198.60	82.46
D0648	2	4	147.63	28.37	176.00	83.88
D0649	12	4	31.38	10.96	42.33	74.12
D0650	12	4	27.76	10.42	38.18	72.70
D0651	12	4	21.85	6.10	27.95	78.18
D0652	12	4	23.52	12.14	35.66	65.95
D0653	24	4	8.32	2.97	11.28	73.69
D0654	24	4	7.91	3.89	11.80	67.05
D0655	24	4	11.38	3.88	15.26	74.59
D0656	24	4	10.43	3.76	14.19	73.50
D0657	72	4	1.40	1.78	3.18	44.01
D0658	72	4	1.81	1.44	3.25	55.60
D0659	72	4	2.03	2.01	4.04	50.25
D0660	72	4	2.03	1.78	3.82	53.26
D0661	120	4	0.68	1.33	2.02	33.94
D0662	120	4	0.86	1.28	2.14	40.15
D0663	120	4	0.12	0.93	1.05	11.42
D0664	120	4	0.71	1.50	2.20	32.02
D0665	168	5	0.56	1.01	1.57	35.67
D0666	168	5	0.80	0.62	1.42	56.43
D0667	168	5	0.91	1.60	2.51	36.14
D0668	168	5	0.62	1.30	1.93	32.36
D0669	168	5	0.34	1.16	1.50	22.51

Brain Single Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0962	0	10	232.98	37.41	270.40	86.16
D0963	0	10	252.65	46.40	299.05	84.49
D0964	0	10	208.58	28.68	237.26	87.91
D0965	0	10	201.61	26.44	228.06	88.40
D0978	2	10	100.67	21.30	121.97	82.53
D0979	2	10	80.06	16.47	96.52	82.94
D0980	2	10	89.07	18.49	107.56	82.81
D0981	2	10	78.01	15.83	93.85	83.13
D0982	12	10	38.49	9.97	48.45	79.43
D0983	12	10	35.40	9.10	44.50	79.55
D0984	12	10	37.34	9.39	46.74	79.90
D0985	12	10	43.90	11.29	55.19	79.55
D0986	24	10	15.00	4.33	19.32	77.61
D0987	24	10	16.25	1.52	17.77	91.43
D0988	24	10	13.94	3.03	16.96	82.15
D0989	24	10	15.44	3.55	18.99	81.30
D0990	72	10	2.70	0.00	2.70	100.00
D0991	72	10	2.27	1.02	3.29	69.08
D0992	72	10	1.74	0.76	2.50	69.75
D0993	72	10	2.78	0.00	2.78	100.00
D0994	120	10	1.79	0.00	1.79	100.00
D0995	120	10	0.39	0.00	0.39	100.00
D0996	120	10	0.82	0.00	0.82	100.00
D0997	120	10	1.05	0.00	1.05	100.00
D0998	168	11	1.02	0.00	1.02	100.00
D0999	168	11	0.98	0.00	0.98	100.00
D1000	168	11	1.02	0.00	1.02	100.00
D1001	168	11	1.48	0.13	1.61	92.18
D1002	168	11	1.69	0.00	1.69	100.00

Kidney Repeat Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0629	0	4	417.21	103.69	520.90	80.09
D0630	0	4	420.51	94.21	514.72	81.70
D0631	0	4	501.73	123.72	625.45	80.22
D0632	0	4	424.38	95.67	520.04	81.60
D0645	2	4	235.50	88.68	324.18	72.65
D0646	2	4	318.76	98.45	417.20	76.40
D0647	2	4	313.10	87.83	400.92	78.09
D0648	2	4	300.05	70.03	370.08	81.08
D0649	12	4	95.52	46.93	142.45	67.05
D0650	12	4	108.39	64.80	173.19	62.59
D0651	12	4	99.34	58.20	157.54	63.06
D0652	12	4	101.72	65.84	167.56	60.71
D0653	24	4	54.14	33.07	87.21	62.08
D0654	24	4	61.57	21.05	82.62	74.52
D0655	24	4	61.55	31.07	92.62	66.45
D0656	24	4	69.22	33.07	102.28	67.67
D0657	72	4	14.32	2.62	16.94	84.53
D0658	72	4	12.45	2.64	15.08	82.52
D0659	72	4	16.56	4.83	21.39	77.41
D0660	72	4	18.48	3.25	21.73	85.05
D0661	120	4	4.62	6.44	11.06	41.80
D0662	120	4	6.33	4.29	10.62	59.63
D0663	120	4	3.25	7.11	10.35	31.36
D0664	120	4	2.51	4.45	6.96	36.09
D0665	168	5	1.97	7.21	9.17	21.46
D0666	168	5	2.86	4.60	7.46	38.31
D0667	168	5	1.37	5.43	6.81	20.19
D0668	168	5	2.75	3.09	5.85	47.10
D0669	168	5	1.48	8.16	9.64	15.38

Kidney Single Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0962	0	10	267.24	78.53	345.77	77.29
D0963	0	10	301.11	87.23	388.34	77.54
D0964	0	10	328.13	87.46	415.59	78.96
D0965	0	10	296.00	85.45	381.46	77.60
D0978	2	10	213.40	69.96	283.36	75.31
D0979	2	10	179.21	73.38	252.59	70.95
D0980	2	10	206.67	76.89	283.56	72.88
D0981	2	10	216.16	69.05	285.21	75.79
D0982	12	10	105.49	65.95	171.44	61.53
D0983	12	10	104.77	51.22	155.99	67.16
D0984	12	10	111.97	59.76	171.73	65.20
D0985	12	10	100.89	50.99	151.88	66.43
D0986	24	10	73.04	33.86	106.91	68.32
D0987	24	10	102.25	46.85	149.10	68.58
D0988	24	10	85.10	37.23	122.32	69.57
D0989	24	10	80.34	38.46	118.80	67.63
D0990	72	10	20.42	13.57	33.98	60.07
D0991	72	10	16.78	16.54	33.32	50.36
D0992	72	10	16.66	13.03	29.69	56.12
D0993	72	10	21.31	16.32	37.63	56.62
D0994	120	10	8.35	7.78	16.13	51.74
D0995	120	10	7.65	7.07	14.72	52.00
D0996	120	10	9.31	8.12	17.43	53.41
D0997	120	10	5.55	7.94	13.48	41.13
D0998	168	11	4.55	4.46	9.01	50.49
D0999	168	11	6.49	5.67	12.16	53.36
D1000	168	11	4.18	5.09	9.26	45.09
D1001	168	11	6.33	6.07	12.40	51.04
D1002	168	11	7.26	7.41	14.67	49.47

Testes Repeat Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0629	0	4	251.16	87.69	338.84	74.12
D0630	0	4	213.93	60.63	274.56	77.92
D0631	0	4	222.38	56.91	279.29	79.62
D0632	0	4	199.06	61.38	260.45	76.43
D0645	2	4	245.68	67.59	313.27	78.42
D0646	2	4	172.48	48.12	220.60	78.19
D0647	2	4	235.43	70.47	305.90	76.96
D0648	2	4	183.21	43.80	227.01	80.71
D0649	12	4	34.60	22.03	56.63	61.10
D0650	12	4	37.13	30.75	67.89	54.70
D0651	12	4	39.44	26.69	66.13	59.64
D0652	12	4	33.62	23.30	56.92	59.06
D0653	24	4	9.28	9.52	18.80	49.35
D0654	24	4	9.39	10.49	19.88	47.22
D0655	24	4	13.56	18.15	31.71	42.77
D0656	24	4	16.44	17.38	33.81	48.61
D0657	72	4	2.54	5.46	7.99	31.73
D0658	72	4	2.47	5.51	7.98	30.97
D0659	72	4	3.38	5.90	9.28	36.42
D0660	72	4	3.94	5.91	9.85	39.96
D0661	120	4	1.68	4.90	6.58	25.48
D0662	120	4	1.82	4.23	6.04	30.05
D0663	120	4	4.61	5.81	10.42	44.26
D0664	120	4	3.20	4.64	7.84	40.87
D0665	168	5	1.28	3.52	4.80	26.63
D0666	168	5	2.36	4.23	6.59	35.79
D0667	168	5	0.59	4.37	4.95	11.86
D0668	168	5	1.23	3.54	4.77	25.85
D0669	168	5	0.95	4.09	5.05	18.91

Testes Single Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0962	0	10	12.99	60.07	73.06	17.77
D0963	0	10	14.50	74.48	88.97	16.29
D0964	0	10	13.79	60.37	74.16	18.59
D0965	0	10	16.12	70.27	86.39	18.66
D0978	2	10	15.01	62.17	77.18	19.45
D0979	2	10	10.76	65.93	76.69	14.03
D0980	2	10	14.38	56.60	70.98	20.26
D0981	2	10	11.89	54.96	66.85	17.78
D0982	12	10	7.35	37.46	44.82	16.41
D0983	12	10	6.38	29.24	35.62	17.92
D0984	12	10	7.86	32.13	39.98	19.65
D0985	12	10	6.47	31.20	37.67	17.18
D0986	24	10	2.92	14.84	17.76	16.42
D0987	24	10	3.30	13.30	16.60	19.86
D0988	24	10	3.06	13.56	16.61	18.39
D0989	24	10	3.33	17.46	20.79	16.03
D0990	72	10	1.24	3.07	4.31	28.69
D0991	72	10	0.87	3.40	4.27	20.46
D0992	72	10	1.61	5.72	7.33	21.91
D0993	72	10	0.81	3.49	4.30	18.79
D0994	120	10	0.45	2.66	3.11	14.57
D0995	120	10	0.48	2.33	2.80	17.04
D0996	120	10	1.05	2.51	3.56	29.41
D0997	120	10	2.09	3.68	5.77	36.27
D0998	168	11	0.51	2.73	3.23	15.63
D0999	168	11	0.48	3.27	3.75	12.81
D1000	168	11	0.40	2.78	3.18	12.66
D1001	168	11	0.61	2.26	2.87	21.31
D1002	168	11	0.54	3.11	3.65	14.92

Liver Repeat Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0629	0	4	1613.11	383.48	1996.59	80.79
D0630	0	4	866.36	NS	866.36	NA
D0631	0	4	1837.66	457.39	2295.04	80.07
D0632	0	4	1516.06	387.20	1903.27	79.66
D0645	2	4	1172.52	698.69	1871.21	62.66
D0646	2	4	782.77	578.42	1361.19	57.51
D0647	2	4	1100.47	720.75	1821.22	60.42
D0648	2	4	776.23	508.67	1284.90	60.41
D0649	12	4	192.81	415.69	608.50	31.69
D0650	12	4	227.84	371.68	599.51	38.00
D0651	12	4	153.07	257.39	410.46	37.29
D0652	12	4	199.27	371.98	571.26	34.88
D0653	24	4	53.56	175.21	228.76	23.41
D0654	24	4	59.00	194.81	253.81	23.25
D0655	24	4	70.61	243.33	313.94	22.49
D0656	24	4	63.94	230.92	294.85	21.68
D0657	72	4	15.50	99.06	114.56	13.53
D0658	72	4	20.18	93.63	113.81	17.73
D0659	72	4	18.80	106.54	125.34	15.00
D0660	72	4	19.10	95.53	114.64	16.66
D0661	120	4	6.70	67.39	74.09	9.05
D0662	120	4	5.86	60.18	66.04	8.88
D0663	120	4	2.08	48.64	50.72	4.10
D0664	120	4	5.11	49.41	54.52	9.37
D0665	168	5	3.12	52.85	55.98	5.58
D0666	168	5	1.52	46.29	47.81	3.18
D0667	168	5	13.40	45.59	58.99	22.71
D0668	168	5	2.16	40.50	42.66	5.05
D0669	168	5	7.68	48.38	56.06	13.70

NS = No Sample

Liver Single Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0962	0	10	967.70	401.56	1369.26	70.67
D0963	0	10	972.69	481.90	1454.59	66.87
D0964	0	10	1078.47	473.48	1551.94	69.49
D0965	0	10	951.50	392.18	1343.68	70.81
D0978	2	10	561.36	562.12	1123.47	49.97
D0979	2	10	475.81	439.91	915.72	51.96
D0980	2	10	476.88	525.53	1002.41	47.57
D0981	2	10	641.62	613.79	1255.41	51.11
D0982	12	10	225.71	491.03	716.75	31.49
D0983	12	10	235.76	424.86	660.62	35.69
D0984	12	10	235.66	490.92	726.58	32.43
D0985	12	10	300.93	532.88	833.81	36.09
D0986	24	10	135.32	221.73	357.05	37.90
D0987	24	10	90.69	303.44	394.14	23.01
D0988	24	10	119.60	255.07	374.67	31.92
D0989	24	10	125.46	257.41	382.86	32.77
D0990	72	10	15.14	106.87	122.02	12.41
D0991	72	10	15.31	97.16	112.47	13.61
D0992	72	10	10.25	87.13	97.38	10.52
D0993	72	10	15.18	99.47	114.65	13.24
D0994	120	10	5.97	55.80	61.77	9.67
D0995	120	10	7.54	50.06	57.60	13.10
D0996	120	10	5.20	75.03	80.23	6.48
D0997	120	10	7.43	58.08	65.51	11.33
D0998	168	11	12.19	43.27	55.46	21.98
D0999	168	11	4.42	41.16	45.58	9.70
D1000	168	11	4.63	43.59	48.22	9.60
D1001	168	11	0.89	43.57	44.46	2.01
D1002	168	11	5.91	57.00	62.91	9.40

Lung Repeat Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0629	0	4	145.15	2.62	147.77	98.23
D0630	0	4	115.18	6.19	121.37	94.90
D0631	0	4	140.84	3.66	144.50	97.47
D0632	0	4	112.81	5.35	118.16	95.47
D0645	2	4	96.32	2.09	98.42	97.87
D0646	2	4	77.00	2.80	79.80	96.49
D0647	2	4	96.81	4.38	101.20	95.67
D0648	2	4	80.94	1.61	82.55	98.05
D0649	12	4	23.27	1.10	24.37	95.49
D0650	12	4	30.72	0.00	30.72	100.00
D0651	12	4	22.53	1.53	24.06	93.63
D0652	12	4	17.95	1.81	19.76	90.86
D0653	24	4	8.63	1.12	9.74	88.56
D0654	24	4	8.38	0.00	8.38	100.00
D0655	24	4	9.24	0.73	9.97	92.66
D0656	24	4	8.35	1.11	9.46	88.27
D0657	72	4	2.74	0.62	3.36	81.54
D0658	72	4	2.47	1.34	3.81	64.88
D0659	72	4	3.49	0.61	4.10	85.05
D0660	72	4	3.38	1.04	4.42	76.48
D0661	120	4	2.17	0.67	2.84	76.32
D0662	120	4	2.65	0.60	3.25	81.47
D0663	120	4	2.10	0.77	2.87	73.33
D0664	120	4	2.21	0.56	2.77	79.69
D0665	168	5	1.98	1.09	3.07	64.43
D0666	168	5	2.24	0.54	2.78	80.46
D0667	168	5	1.25	0.81	2.06	60.81
D0668	168	5	1.97	0.00	1.97	100.00
D0669	168	5	1.92	0.28	2.20	87.41

Lung Single Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0962	0	10	82.10	18.63	100.73	81.51
D0963	0	10	99.16	21.17	120.33	82.41
D0964	0	10	89.00	18.55	107.55	82.75
D0965	0	10	97.49	20.80	118.29	82.42
D0978	2	10	62.74	16.60	79.33	79.08
D0979	2	10	60.34	24.09	84.43	71.46
D0980	2	10	41.32	16.27	57.59	71.75
D0981	2	10	68.68	21.86	90.55	75.85
D0982	12	10	29.72	15.77	45.49	65.34
D0983	12	10	21.34	13.72	35.06	60.86
D0984	12	10	31.36	15.50	46.86	66.93
D0985	12	10	29.34	13.84	43.19	67.95
D0986	24	10	11.89	8.94	20.83	57.10
D0987	24	10	9.08	10.09	19.18	47.37
D0988	24	10	9.82	8.72	18.53	52.96
D0989	24	10	2.37	10.12	12.49	19.00
D0990	72	10	0.28	6.24	6.52	4.31
D0991	72	10	2.60	5.98	8.58	30.30
D0992	72	10	1.39	7.48	8.87	15.70
D0993	72	10	1.72	6.42	8.14	21.15
D0994	120	10	0.19	4.27	4.46	4.15
D0995	120	10	0.73	5.44	6.17	11.86
D0996	120	10	0.64	5.47	6.11	10.48
D0997	120	10	5.69	4.51	10.20	55.80
D0998	168	11	0.60	4.48	5.08	11.76
D0999	168	11	0.29	3.96	4.25	6.85
D1000	168	11	0.77	4.03	4.79	16.02
D1001	168	11	0.00	4.71	4.71	0.02
D1002	168	11	1.50	4.47	5.97	25.10

Fat Repeat Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0629	0	4	354.39	27.40	381.79	92.82
D0630	0	4	393.87	30.83	424.70	92.74
D0631	0	4	652.36	99.65	752.01	86.75
D0632	0	4	553.36	54.37	607.73	91.05
D0645	2	4	No Smpl	No Smpl	No Smpl	No Smpl
D0646	2	4	555.82	58.71	614.54	90.45
D0647	2	4	736.69	102.69	839.39	87.77
D0648	2	4	412.29	62.80	475.10	86.78
D0649	12	4	569.44	189.08	758.52	75.07
D0650	12	4	145.04	13.83	158.87	91.29
D0651	12	4	294.95	45.10	340.06	86.74
D0652	12	4	274.85	48.36	323.21	85.04
D0653	24	4	166.38	19.43	185.81	89.55
D0654	24	4	263.74	24.34	288.08	91.55
D0655	24	4	172.63	16.17	188.79	91.44
D0656	24	4	299.51	48.61	348.12	86.04
D0657	72	4	41.06	4.78	45.84	89.57
D0658	72	4	69.66	8.54	78.20	89.08
D0659	72	4	66.35	8.32	74.67	88.86
D0660	72	4	75.49	6.75	82.24	91.79
D0661	120	4	34.52	4.84	39.36	87.70
D0662	120	4	16.26	1.78	18.04	90.16
D0663	120	4	11.70	0.81	12.50	93.55
D0664	120	4	17.37	2.11	19.49	89.17
D0665	168	5	38.54	5.12	43.66	88.28
D0666	168	5	21.45	2.01	23.46	91.42
D0667	168	5	17.95	2.53	20.48	87.63
D0668	168	5	16.26	2.45	18.71	86.88
D0669	168	5	21.77	5.06	26.82	81.15

Fat Single Extraction Efficiency

Animal ID	Time Pt.	Group	ug eq HMDS extract	ug eq HMDS Pellet	Total ug eq HMDS	Percent of Total Extracted
D0962	0	10	461.04	35.53	496.57	92.85
D0963	0	10	523.71	33.41	557.12	94.00
D0964	0	10	549.70	46.58	596.28	92.19
D0965	0	10	744.74	68.06	812.80	91.63
D0978	2	10	553.21	52.23	605.44	91.37
D0979	2	10	658.86	72.94	731.80	90.03
D0980	2	10	754.10	93.73	847.83	88.94
D0981	2	10	278.11	13.00	291.11	95.54
D0982	12	10	557.58	111.61	669.18	83.32
D0983	12	10	505.28	64.23	569.51	88.72
D0984	12	10	401.07	38.25	439.31	91.29
D0985	12	10	332.56	45.00	377.56	88.08
D0986	24	10	354.27	42.42	396.69	89.31
D0987	24	10	315.09	35.24	350.33	89.94
D0988	24	10	348.50	32.00	380.49	91.59
D0989	24	10	393.98	62.95	456.93	86.22
D0990	72	10	115.51	14.95	130.46	88.54
D0991	72	10	98.08	9.29	107.37	91.35
D0992	72	10	82.66	14.16	96.82	85.38
D0993	72	10	122.18	19.13	141.31	86.46
D0994	120	10	55.73	8.18	63.92	87.19
D0995	120	10	54.03	9.27	63.30	85.35
D0996	120	10	40.94	4.58	45.52	89.93
D0997	120	10	67.29	8.91	76.20	88.30
D0998	168	11	35.65	3.83	39.48	90.30
D0999	168	11	27.43	1.74	29.17	94.04
D1000	168	11	38.10	3.26	41.36	92.12
D1001	168	11	50.88	6.95	57.83	87.99
D1002	168	11	47.30	6.17	53.47	88.47

APPENDIX D – Statistical Analysis

This document contains the statistical analysis of the data from Study 9829, which was completed August 28, 2006.

Signature Cynthia Van Landingham Date Dec 5, 2006

Data

Data for this analysis came from two studies in Fischer 344 rats:

1. 14-day nose-only vapor inhalation exposure to HMDS followed by an exposure to ^{14}C-HMDS on day 15 (labeled the repeat study)
2. single nose-only vapor inhalation exposure to ^{14}C-HMDS (labeled the single study).

For each of these studies data was received for levels of the parent compound and the radiolabeled compound at times ranging from the end of exposure up to 7 days post-exposure. Measurements were taken in the following tissues:

1. blood
2. the tissues of the lung, liver, kidney, brain, testes and fat
3. charcoal tubes
4. feces and urine (radiolabeled compound only)
5. potassium hydroxide (KOH) (radiolabeled compound only)

Methods

All analysis was done with SAS version 9.13 [1].

Areas under the curve (AUCs) were calculated for both the radiolabeled and the parent compound using Bailer's method which produces both a mean and a standard error. These statistics were used to calculate upper and lower confidence limits on the AUCs. Comparisons between the parent and radiolabeled compound AUCs in the charcoal tubes, blood and the tissues of the lung, liver, kidney, brain, testes and fat were done using the values from the Bailer method [2] and the Satterthwaite [3] approximation method.

A half-life was computed for the parent and radiolabeled compounds in each of the media in which it was sampled. In some cases, multiple half-lives were computed over different time periods. The specific time periods used for each half-life calculation are specified in Table 5.

Results

Calculated values for the standard error, degrees of freedom, Mean AUC and lower and upper confidence limits for the AUC are given in Tables 1 and 2 for the ^{14}C-HMDS and the HMDS respectively. The comparisons of the HMDS AUC to the ^{14}C-HMDS AUC by tissue/media are given in given in Table 3. In every case, the comparison of the HMDS AUC to the ^{14}C-HMDS AUC shows a statistically significant difference with p-values of < 0.001. The comparison of the single study AUC to the repeat study AUC for each compound (HMDS and ^{14}C-HMDS) are given in Table 4. The comparisons show that the blood, brain, lung and liver HMDS AUCs and the liver and urine ^{14}C-HMDS AUCs are not statistically different between the repeat study and the single study. The comparisons in all other tissues/media for HMDS and for ^{14}C-HMDS show a statistically significant difference between the AUCs calculated from the single study data and the corresponding AUCs from the repeat study data.

The half-lives for the parent (HMDS) and radiolabeled (^{14}C-HMDS) compounds in the different tissues and media over different time intervals are given in Table 5.

Table 1

AUCs for ^{14}C-HMDS

Study	Tissue/ Media	Standard Error	Degrees Freedom	Lower 95% CL (µg Eq/g)	Mean Area Under the Curve (µg Eq/g)	Upper 95% CL (µg Eq/g)
Repeat	Blood	50.12	4.2320	1305.30	1441.49	1577.67
Repeat	Brain	51.63	5.1851	1118.41	1249.72	1381.03
Repeat	Fat	2411.80	6.7912	36932.50	42671.25	48410.00
Repeat	Kidney	95.54	12.8690	4772.64	4979.26	5185.88
Repeat	Liver	121.91	8.7291	3661.55	3938.64	4215.72
Repeat	Lung	39.97	6.7704	1547.41	1642.58	1737.75
Repeat	Testes	63.79	8.8804	1540.47	1685.07	1829.68
Single	Blood	33.80	6.4048	807.53	888.99	970.45
Single	Brain	26.64	8.8489	1008.62	1069.05	1129.48
Single	Fat	1747.71	9.4898	54167.32	58090.02	62012.73
Single	Kidney	158.90	4.3592	5262.98	5690.18	6117.38
Single	Liver	70.18	14.3185	4074.84	4225.04	4375.24
Single	Lung	109.38	10.4937	2447.02	2689.18	2931.34
Single	Testes	22.04	10.2190	630.41	679.37	728.34
Repeat	Charcoal	420.44	25.3541	21294.93	22160.23	23025.52
Single	Charcoal	527.79	19.4929	28213.31	29316.10	30418.89
Repeat	Feces	406.12	9.0337	5745.85	6664.03	7582.22
Repeat	KOH	51.70	6.3422	1430.23	1555.10	1679.98
Repeat	Urine	4697.34	8.2683	78193.77	88964.98	99736.19
Single	Feces	605.08	5.5403	7086.28	8597.15	10108.03
Single	KOH	68.76	4.2923	906.54	1092.43	1278.33
Single	Urine	2370.84	14.1474	95149.83	100229.81	105309.79

Table 2

AUCs for HMDS

Study	Tissue/ Media	Standard Error	Degrees Freedom	Lower 95% CL (µg/g)	Mean Area Under the Curve (µg/g)	Upper 95% CL (µg/g)
Repeat	Blood	2.01	3.2046	35.74	41.91	48.07
Repeat	Brain	3.37	6.8111	129.01	137.03	145.05
Repeat	Fat	6070.71	7.2762	79813.24	94058.48	108303.71
Repeat	Kidney	113.04	8.4166	2822.62	3081.05	3339.48
Repeat	Liver	9.74	5.4685	74.43	98.85	123.27
Repeat	Lung	16.71	7.6805	331.10	369.91	408.72
Repeat	Testes	165.08	8.0291	366.79	747.22	1127.66
Single	Blood	1.40	4.6993	43.51	47.17	50.83
Single	Brain	6.15	3.8509	107.18	124.51	141.84
Single	Fat	1825.82	9.7167	43854.57	47938.90	52023.22
Single	Kidney	109.66	4.8999	1914.74	2198.38	2482.02
Single	Liver	14.91	3.5370	25.95	69.58	113.21
Single	Lung	48.85	4.1221	269.64	403.72	537.79
Single	Testes	56.12	7.6239	96.09	226.62	357.14
Repeat	Charcoal	777.15	7.6265	24837.54	26645.03	28452.53
Single	Charcoal	239.38	18.3275	13319.58	13821.85	14324.12

Table 3

Comparison of ^{14}C-HMDS and HMDS AUCs

Study	Tissue/ Media	Mean Diff. in AUC (^{14}C HMDS - HMDS)	Mean Diff. Standard Error	Degrees of Freedom	T statistic	Two-sided p-value $\|T\| > t$
Repeat	Blood	1399.58	50.16	4.25	27.90	<0.0001
Repeat	Brain	1112.69	51.74	5.23	21.51	<0.0001
Repeat	Fat	-51387.23	6532.25	9.50	-7.87	<0.0001
Repeat	Kidney	1898.21	148.00	18.55	12.83	<0.0001
Repeat	Liver	3839.79	122.30	8.84	31.40	<0.0001
Repeat	Lung	1272.67	43.32	9.10	29.38	<0.0001
Repeat	Testes	937.85	176.98	10.40	5.30	0.0003
Single	Blood	841.82	33.83	6.43	24.88	<0.0001
Single	Brain	944.54	27.34	9.75	34.54	<0.0001
Single	Fat	10151.13	2527.47	19.19	4.02	0.0007
Single	Kidney	3491.80	193.07	7.91	18.09	<0.0001
Single	Liver	4155.46	71.74	15.51	57.92	<0.0001
Single	Lung	2285.47	119.79	13.71	19.08	<0.0001
Single	Testes	452.76	60.29	9.98	7.51	<0.0001
Repeat	Charcoal	-4484.80	883.59	12.42	-5.08	0.0002
Single	Charcoal	15494.26	579.54	27.12	26.74	<0.0001

Table 4

Comparison of Repeat Study and Single Study AUCs by Compound Type

Compound Type	Tissue/ Media	Mean Diff. in AUC (repeat – single)	Mean Diff. Standard Error	Degrees of Freedom	T Statistic	Probability |T| > t
HMDS	Blood	-5.27	2.45	6.082	-2.152	0.074
	Brain	12.52	7.01	6.199	1.786	0.123
	Fat	46119.58	6339.33	8.599	7.275	<0.001
	Kidney	882.67	157.49	12.577	5.605	<0.001
	Liver	29.27	17.81	6.443	1.643	0.148
	Lung	-33.81	51.63	5.105	-0.655	0.541
	Testes	520.61	174.36	9.853	2.986	0.014
	Charcoal	12823.19	813.18	9.108	15.769	<0.001
^{14}C-HMDS	Blood	552.49	60.45	7.881	9.140	<0.001
	Brain	180.67	58.10	7.983	3.110	0.014
	Fat	-15418.77	2978.47	13.193	-5.177	<0.001
	Kidney	-710.92	185.41	7.738	-3.834	0.005
	Liver	-286.40	140.66	14.502	-2.036	0.060
	Lung	-1046.60	116.45	13.121	-8.988	<0.001
	Testes	1005.70	67.49	10.991	14.901	<0.001
	Charcoal	-7155.87	674.78	39.769	-10.605	<0.001
^{14}C-HMDS	Feces	-1933.12	728.74	10.366	-2.653	0.024
	KOH	462.67	86.03	8.647	5.378	<0.001
	Urine	-11264.83	5261.74	12.542	-2.141	0.053

Table 5
Half-Lives

		HMDS			^{14}C-HMDS		
Tissue/ Media	**Study**	**Time Interval (hrs)**	**Half-life (hrs)**	**Mean Square Error**	**Time Interval (hrs)**	**Half-life (hrs)**	**Mean Square Error**
Blood	Single	0-2	0.555	0.517	2-24	10.802	0.009
		12-24 + 72	58.905	0.015	72-168	77.318	0.266
					24-168	36.468	0.537
	Repeat	0-2	0.506	0.580	2-24	5.701	0.280
		12-24 + 72	36.869	0.059	72-168	86.953	0.144
					24-168	38.610	0.475
Brain	Single	0-12	1.771	1.209	0-2	1.391	0.000
		0-2	0.561	0.000	0-24	5.603	0.488
		12-168	24.316	0.437	12-168	23.938	0.833
					24-168	29.963	0.688
	Repeat	0-12	1.714	1.266	0-12	3.568	0.193
		0-2	0.538	0.000	0-24	4.666	0.393
		12-168	26.345	0.375	24-168	41.154	0.440
Fat	Single	0-168	21.900	0.060	0-168	35.041	0.315
	Repeat	2-168	19.284	0.252	2-168	29.891	0.394
Kidney	Single	0-2	1.196	0.000	0-12	8.537	0.152
		2-168	23.095	0.178	12-168	36.703	0.296
	Repeat	0-2	1.050	0.000	0-12	6.456	0.098
		2-168	24.366	0.099	12-168	30.255	0.522
Liver	Single	0-2	0.502	0.000	0-24	11.970	0.140
		12-168	19.560	0.709	24-168	42.378	0.406
	Repeat	0-2	0.338	0.000	0-12	5.755	0.005
		12-168	20.881	0.929	0-24	7.409	0.212
					24-168	51.270	0.236
Lung	Single	0-2	1.408	0.000	0-12	7.333	0.166
		12-120	15.971	0.787	24-168	59.245	0.265
	Repeat	0-2	0.770	0.000	0-12	4.747	0.064
		12-168	18.168	0.877	24-168	61.765	0.234
Testes	Single	0-2	0.742	0.000	0-12	11.258	0.024
		12-168	39.778	0.301	24-168	48.674	0.417
	Repeat	0-12	3.414	0.234	0-12	5.343	0.115
		24-168	51.327	0.721	24-168	55.854	0.271
Charcoal	Single	1-6	1.596	0.346	1-6	1.628	0.347
		12-168	18.824	0.264	12-168	18.972	0.264
	Repeat	1-6	1.509	0.368	1-6	1.567	0.399
		12-168	21.714	0.193	12-168	18.549	0.292
Feces	Single				24-168	16.061	0.592
	Repeat				24-168	19.429	0.634
Urine	Single				12-168	17.661	0.475
	Repeat				12-168	15.321	0.786
KOH	Single				24-168	21.710	0.600
	Repeat				24-168	16.728	0.926

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